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THE RESISTANCE OF FOWL TO STRYCHNINE*

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THE statement is made quite generally in textbooks of pharmacology[1, 2, 3] that fowl tolerate large quantities of strychnine without toxic effects. In keeping with this, strychnine has been widely used to kill destructive rodents, with the belief that fowl or game which ingest the drug would not be injured.

The present investigation is a study of the resistance of fowl to strychnine. In the first part of the work, both chickens and pigeons were used, but later, because of the cost and the fact that similar results were obtained from the two types, pigeons were used exclusively. Strychnine sulphate was the preparation of the alkaloid used. It was given subcutaneously, and also by mouth in solution and in solid form.

Knowing that the presence of food in the alimentary tract might influence the rate of absorption, the strychnine was administered to some birds after feeding, and to some after several hours of starvation. Since strychnine spasms cause glycogen to disappear from the liver and ultimately reduces the blood sugar, the effect of glucose feeding on strychnine spasm also was studied. The details of each procedure are recorded in the protocols.

METHODS AND RESULTS

A. *Normal Pigeons.*—These were given cracked corn and water *ad libitum.* When the drug was given per os in solution, the dose was dissolved in 5 c.c. of distilled water and introduced directly into the crop through a catheter. When solid strychnine was used, it was given in the form of hypodermic tablets, placed directly into the crop by means of forceps. Fluid was withheld

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from the birds to which solid strychnine was given. When given subcutaneously, the dose of the drug was dissolved in ½ c.c. of distilled water and injected under the skin in the pectoral region.

It was found after a series of preliminary experiments that the minimum lethal dose when given subcutaneously was about 2 mg. per kilo. When given by mouth the M.L.D. was 23.50 mg. per kilo when in a solution, and 30 mg. per kilo when given in solid form.

B. *Starved Pigeons.*—In this series the pigeons were starved for twenty-four to forty-eight hours previous to the experiment—water being allowed—in order to determine the effect of starvation on strychnine action. Administration of strychnine was the same as in the fed birds, subcutaneously and by mouth in solution or in solid form.

It was found that the M. L. D. subcutaneously was 1.5 mg. per kilo, while in solution per os it was 18.50 mg. per kilo, and 20 mg. per kilo when given in solid form. The M. L. D. in starved fowl is slightly less than in fed ones.

C. *With Glucose.*—Glucose was administered in a 20 per cent solution, 10 to 20 c.c. being given every hour for three hours. Then after a period of four hours, during which time a quantity of the carbohydrate might have been converted into glycogen in the liver, strychnine was given subcutaneously and in solid form as described in section A.

It can be seen from Table I that the M. L. D. under both conditions is markedly increased. Subcutaneously the M. L. D. is 6.75 mg. per kilo, and when given in solid form per mouth it was about 70 mg. per kilo. A solution of strychnine per os was not used after glucose, since the crop was filled with fluid and the drug went into solution quickly.

PROTOCOL I

SUBCUTANEOUS INJECTION; FED FOWL; STRYCHNINE SULPHATE

PIGEON	WEIGHT IN GRAMS	DOSE IN MG. PER KILO	REACTION
1.	285	0.50	Recovery
2.	305	1.00	Recovery
3.	293	1.50	Recovery
4.	280	2.00	Death
5.	300	2.50	Death
6.	315	2.00	Death
7.	302	1.50	Recovery
8.	284	2.00	Death

M. L. D. 2.00 mg. per kilo.

PROTOCOL II

SUBCUTANEOUS INJECTION; STARVED FOWL; STRYCHNINE SULPHATE

PIGEON	WEIGHT IN GRAMS	DOSE IN MG. PER KILO	REACTION
1.	306	0.50	Recovery
2.	297	1.00	Recovery
3.	287	1.50	Recovery
4.	309	2.00	Death
5.	288	1.75	Death
6.	296	1.50	Death
7.	285	1.50	Death
8.	293	1.50	Death

M. L. D. 1.50 mg. per kilo.

PROTOCOL III

SUBCUTANEOUS INJECTION; FED FOWL AND AFTER GLUCOSE

PIGEON	WEIGHT IN GRAMS	DOSE IN MG. PER KILO	REACTION
1.	312	0.50	Recovery
2.	294	1.00	Recovery
3.	306	2.00	Recovery
4.	280	4.00	Recovery
5.	272	6.00	Recovery
6.	298	8.00	Death
7.	304	7.00	Death
8.	268	6.50	Recovery
9.	292	6.75	Death
10.	287	6.75	Death
11.	280	6.50	Recovery
12.	293	6.75	Death

PROTOCOL IV

DRUG GIVEN BY MOUTH IN SOLUTION; FED FOWL

PIGEON	WEIGHT IN GRAMS	DOSE IN MG. PER KILO	REACTION
1.	295	0.50	Recovery
2.	311	1.00	Recovery
3.	306	2.00	Recovery
4.	299	4.00	Recovery
5.	300	8.00	Recovery
6.	305	16.00	Recovery
7.	297	25.00	Death
8.	286	20.00	Recovery
9.	290	22.00	Recovery
10.	297	24.00	Death
11.	293	23.00	Recovery
12.	312	23.50	Death
13.	280	23.50	Death

M. L. D. 23.50 mg. per kilo.

PROTOCOL V

DRUG GIVEN BY MOUTH; STARVED FOWL

PIGEON	WEIGHT IN GRAMS	DOSE IN MG. PER KILO	REACTION
1.	295	10.00	Recovery
2.	306	15.00	Recovery
3.	311	20.00	Death
4.	299	17.00	Recovery
5.	307	18.00	Recovery
6.	302	19.00	Death
7.	305	18.50	Death
8.	283	18.50	Death
9.	288	18.50	Death

M. L. D. 18.50 mg. per kilo.

PROTOCOL VI

DRUG GIVEN IN SOLID FORM; FED PIGEONS

PIGEON	WEIGHT IN GRAMS	DOSE IN MG. PER KILO	REACTION
1.	309	10.00	Recovery
2.	312	20.00	Recovery
3.	304	30.00	Death
4.	287	25.00	Recovery
5.	295	28.00	Recovery
6.	283	29.00	Recovery
7.	298	30.00	Recovery
8.	308	30.00	Death
9.	300	30.00	Death

M. L. D. 30.00 mg. per kilo.

PROTOCOL VII

DRUG GIVEN IN SOLID FORM; STARVED FOWL

PIGEON	WEIGHT IN GRAMS	DOSE IN MG. PER KILO	REACTION
1.	304	10.00	Recovery
2.	310	20.00	Death
3.	296	18.00	Recovery
4.	284	19.00	Recovery
5.	278	20.00	Recovery
6.	298	20.00	Death
7.	283	20.00	Death

M. L. D. 20.00 mg. per kilo.

PROTOCOL VIII

DRUG GIVEN IN SOLID FORM TO FOWL FED WITH GLUCOSE

PIGEON	WEIGHT IN GRAMS	DOSE IN MG. PER KILO	REACTION
1.	297	10.00	Recovery
2.	307	20.00	Recovery
3.	304	30.00	Recovery
4.	297	40.00	Recovery
5.	295	50.00	Recovery
6.	278	60.00	Recovery
7.	296	70.00	Recovery
8.	286	75.00	Death
9.	294	70.00	Death
10.	289	72.00	Death
11.	295	70.00	Recovery
12.	289	69.00	Death

M. L. D. about 70.00 mg. per kilo.

Pigeons that recovered were used a second time only after a period of two weeks, that time being allowed for total excretion of strychnine. The appended protocols show the method of determining the M. L. D.

The accompanying table (IX) summarizes the results obtained.

SUMMARY IX

METHOD OF ADMINISTRATION	FORM OF STRYCHNINE	CONDITION OF FOWL	REMARKS	M. L. D.
Subcutaneous	Solution	Fed	—	2.00
Subcutaneous	Solution	Starved	—	1.50
Subcutaneous	Solution	Fed	After glucose	6.75
Mouth	Solution	Fed	—	23.50
Mouth	Solution	Starved	—	18.50
Mouth	Solid	Fed	—	30.00
Mouth	Solid	Starved	—	20.00
Mouth	Solid	Fed	Glucose	70.00

M. L. D. is expressed in milligrams per kilo body weight.

DISCUSSION

Several explanations have been offered for the disintoxication of strychnine in fowl. Londini[4] believed that cholesterol in some way disintoxicated strychnine. Salant[5] found that when strychnine was added to the contents of the large intestine it could not be identified, stating that the substances present destroyed the drug. Hatcher's findings[6] were at variance with Salant's.

Kobert[7] states that with a large dose of strychnine, from 50 to 75 per cent can be recovered unchanged. While Ipsen (Kobert, p. 1157) believed

that strychnine in the liver was not contained in the cell but in the blood, later work[8, 9] has indicated that strychnine is actually destroyed in the liver or held in loose combination there. Although excretion is rather rapid, strychnine has been found in cadavers even after a period of a year.[10]

It is stated[2] that the increased muscular tone and convulsions cause an increased use of glycogen which[3] disappears from the liver in most animals. Repeated doses of strychnine produce quicker and more lasting results in the frog.[11] This last result may be due to two things: first, an increased susceptibility of the spinal cord, or second, inability of the animal to destroy the poison. However, these authors could not detect strychnine in the control animal. Both factors may play a part in cases where sufficient time is not allowed for complete excretion or destruction of the alkaloid.

The inability of the liver to destroy strychnine may be due to either an overwhelming dose, or to a decreased amount of neutralizing substance in the organ, or to a decreased function of the cells due to lack of nutrition. The first fact is controllable. The second is dependent on the third. The elaboration of a neutralizing substance by the liver cell is subject to the nutrition of the cell.

The fact that the M. L. D. for starved fowl is less than for fed ones seems due to a quicker absorption. In the well-fed animal also, larger doses of strychnine might be administered without toxic effects if the liver has optimum nutrition. Since glucose is most easily and quickly assimilated, we introduced this substance into the crop and found that after a period of six hours the M. L. D., both by mouth and subcutaneously, was markedly increased, see Summary (IX).

The results indicate that pigeons and chickens possess an immunity to strychnine only when it is given by mouth. While the M. L.D. given subcutaneously is relatively higher than the M. L. D. for most laboratory animals, it is lower than that for the guinea pig, frog, and adder.[12]

When this drug is given by mouth the M. L. D. is markedly higher. Without doubt the amount of food in the crop is a most important factor. The greater the quantity of food in the crop, the slower the rate of absorption of the drug, and hence the liver, which is perhaps the chief site of disintoxication, is not overwhelmed and filters the noxious material from the blood stream.

The condition of the liver is a second factor and probably the more important. When a fowl is starved for forty-eight hours, the crop becomes empty and the store of glycogen in the liver is called upon to furnish food. Strychnine is more active under this condition. Thus, it would seem that the ability of the liver to disintoxicate strychnine depends to some extent on the glycogen content. This consideration would also explain the fact that hashed liver destroys only a small part of the strychnine mixed with it[8] since the glycogen quickly disappears from excised tissue.

CONCLUSIONS

1. Fowl possess a relative immunity to strychnine only when the drug is given by mouth.

2. The M. L. D. depends on the contents of the crop, the rate of absorption being inversely proportional to the amount of food in the crop and directly proportional to its fluidity.

3. Glucose, presumably by increasing the glycogen content of the liver, enables the animal to withstand a larger dose. This is not understood, but it may be due directly to the glycogen or its elaboration of a neutralizing agent.

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THE BLOOD SEDIMENTATION TEST (FAHRAEUS) IN THE DIAGNOSIS AND PROGNOSIS OF DISEASE*

By M. Bochner, M.B. (Tor.), and H. Wassing, M.D., Paterson, N. J.

HISTORY

In 1918, Robin Fahraeus of Stockholm, working in the Physiological Institute of the University of Kiel, published experiments concerning the velocity of sedimentation in the citrated blood of pregnant women in comparison to the sedimentation velocity of citrated blood in nongravid women and in men.

This has led to a great deal of further investigation of this phenomenon, which corresponds to the crumsta phlogistica of Galen and which is so admirably described by John Hunter in his book, "On the Blood, Inflammation, and Gun-shot Wounds." This great English physician, as early as 1797 speaks of the increased tendency of the red cells to sedimentation which he observed in the shed blood of patients suffering from inflammatory conditions, and that the rapidity of the process was in relationship to the severity of the infection. This phenomenon played a most important part up to the end of the eighteenth century and was almost the only blood symptom to which attention was given. It had been so entirely forgotten in the last decades of the nineteenth century, since Virchow's cellular pathology brought about a complete change in our comprehension of disease, that Fahraeus was wholly unconscious of only having found a better method of observing a

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phenomenon which had been known to Hippocrates; namely, the appearance of the so-called buffy coat or buffy crust of the Greeks, the crusta inflammatoria on the surface of shed blood of patients suffering from inflammatory conditions which did not secrete itself but remained in the blood cake of healthy individuals.

The nature of the shed blood was the prototype for the ancient humoral pathology (*Fahraeus' Review of the History of the Buffy Coat*). Diseases were supposed to have arisen from the cessation of the normal mixture of the four fluids composing the blood: first, the black bile or melancholia, the dark lower part of the blood cake; second, the blood in the limited sense of antiquity (sanguis), the upper portion of the blood cake; third, the yellow bile, gradually freeing itself (the expressed serum); and fourth, the phlegm. The phlegm did not secrete itself spontaneously in healthy blood, but was present in the blood cake. The Greeks knew that by shaking healthy blood the phlegm could be separated and the whole prevented from clotting. In unhealthy blood, however, the phlegm collected in a more or less thick layer on the top of the blood cake, which was, of course, interpreted as being a consequence of this substance having increased.

Fahraeus has given a beautiful description of the entire history of the buffy coat. Until Hunter, there was only the one theory explaining the appearance of the buffy crust; namely, increase of what the Greeks called phlegm. Hunter, who tried the most ingenious experiments on the buffy coat, as for instance, mixing quick sedimentating blood with serum from slow sedimentating blood and vice versa, came to the conclusion that the formation of the buffy coat depends upon the increased quantity of fibrin and on the increased tendency of the red cells to separation; a conception which conforms to all that capillar-electricity, colloid chemistry, and capillary microscopy brought out regarding this phenomenon in the last five years. How is it to be explained that modern science has not taken up the subject of the buffy crust in its annals, other than as an historical curiosity?

The reaction against the humoral pathology through Virchow's cellular pathology was so violent, that one never gave oneself time to prove the observations of our elders respecting the gross appearance of the blood in its true light. It is quite characteristic that at a time when the appearance of the buffy coat in blood of pregnant women had been forgotten, the increase of leucocytes in the blood during pregnancy was discovered, and so, through this complete discarding of humoral pathology, we can more readily understand why Fahraeus, Linzenmeier and others, who undoubtedly had seen hundreds of Wassermann blood specimens in the racks or ice boxes of their laboratories, taken from patients with and without inflammatory conditions, some showing coagulation of the fluid in toto, while others showed separation of the bluish transparent lymph (Hunter) on the surface, had taken no notice of it. When they first observed the difference in sedimentation velocity of the red cells in pregnancy and inflammatory conditions, it appeared new to them. Only *following* their observation, did they discover that the conception of the blood sedimentation, almost in its modern form, had already been familiar to Hunter.

There is no doubt that for exact laboratory purposes and clinical application only the observation of sedimentation in blood, mechanically prevented from coagulation, can be used and it is to the credit of Fahraeus[1] to have introduced this method, and to Linzenmeier,[2] of Leipzig, for having applied this test in the clinical observation of gynecologic and subsequently of inflammatory conditions in general.

TECHNIC

Prior to discussing the clinical value of the test the following is a brief description of the technic as used by us in the laboratory of the Barnert Memorial Hospital. Essentially, it is a modification of the technic as described by Linzenmeier.[3] We use small tubes (Fig. 1), resembling centrifuge tubes, of 6 mm. inner diameter, which are graduated downwards from the 1 c.c. mark into lines of 3 mm. distance for 18 mm. To this tube is added 0.2 c.c. of a 2 per cent solution of sodium citrate. One c.c. of blood from a

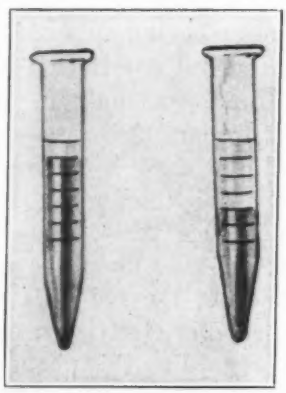

Fig. 1.—Red cell sedimentation after ten minutes; *left*, normal person, sedimentation down to line 3 mm.; *right*, acute appendicitis, sedimentation down to line 12 mm. Tubes in picture are ¾ of natural size.

vein is drawn up into a dry syringe or syringe rinsed with citrate (Fig. 2) and is immediately added to the citrate in the tube, drop by drop, to prevent the formation of air bubbles, until the 1 c.c. mark is reached. The contents of the tube are mixed either by inverting, or better still, by carefully drawing the contents up and down a few times by means of a fine pipette (Fig. 3). This insures thorough mixing without loss of any fluid. For this reason it is superior to mixing the blood and citrate in the syringe. The tubes are now allowed to stand in a vertical position and the reading made when line No. 12 is reached,—in other words, when the red cells have settled down to the line indicating that the height of the column of supernatant plasma is 12 mm. As this test is still in the experimental stage, and no definite standard technic or apparatus adopted, we can readily understand that various investigators use different readings—some very complicated ones. Line No. 18 is the most popular standard at present, but while we do not consider it inferior to line No. 12 there is no doubt that the latter has certain advantages when used as a routine in clinical work. First, the most marked sedimentation velocity

is manifest up to line No. 12; from then on, the sedimentation becomes gradually slower, as observed in the curve, e.g., line No. 12 in fifteen minutes and line No. 15 in one hour. Secondly, in many cases of retarded sedimentation line No. 12 is the lowest index reached within two hours. Thirdly, since the greatest use of this test is in its clinical application, speed without

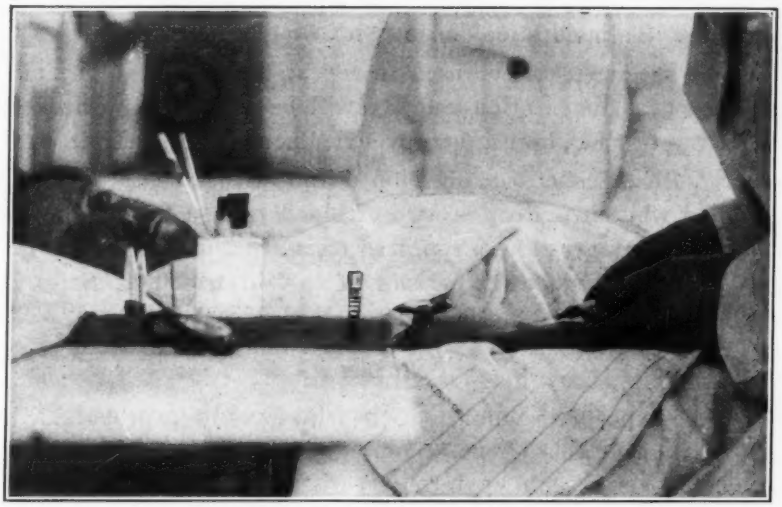

Fig. 2.

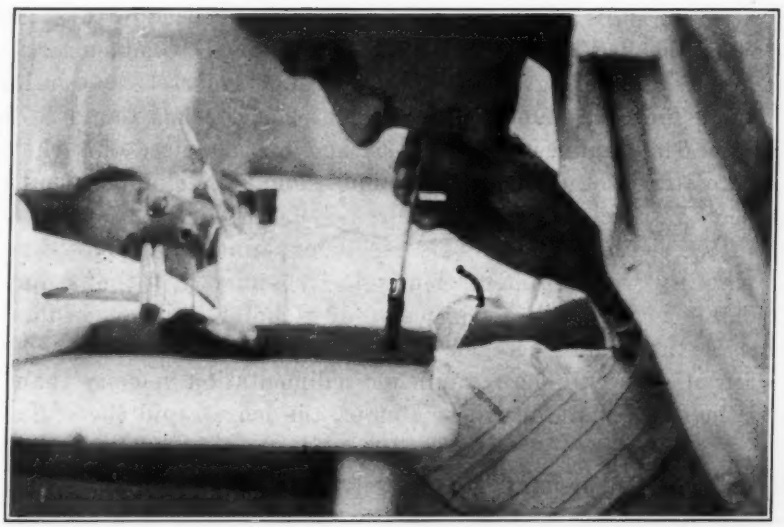

Fig. 3.—Mixing blood with sodium citrate.

sacrifice of accuracy and correct interpretation, is manifestly an asset. Normal individuals in line No. 12 interpretation are those whose sedimentation velocity is 130 minutes or over; in line No. 18 interpretation those whose sedimentation velocity is 600 minutes or more. In other words, line No. 12 gives as accurate an observation in a much shorter time.

Plotting a curve, with the sedimentation readings as abscissa and the

time of reading as ordinate, gives a very striking picture of the sedimentation velocity at the different stages of the test. To standardize these various methods of sedimentation readings we desire to recommend the use of the sedimentation ratio of the sedimentation velocity *found,* with that of the normal for the same sex, e.g., case of acute appendicitis, female; line No. 12 reached in twelve minutes. Average of healthy women with same method is 130 minutes. Sedimentation Ratio (SR) = 1/13.

The same specimen can be used to repeat the test by remixing and the same readings of sedimentation velocity will be obtained. (An excellent description of the test has been given by Friedlaender,[4] of Detroit.)

Recently, Linzenmeier[5] has developed and advocated the use of a micrometric method wherein a drop or two of blood from a finger is sufficient for the test. Its advantages, where repeated tests are indicated are quite obvious since it eliminates frequent punctures of a vein which at times, are both undesirable and difficult, especially in small children.

THEORY

As is to be expected a number of theories have been propounded to serve as an explanation of this phenomenon. It is doubtful, however, if any one explanation, by itself, can be termed satisfactory. Fahraeus[6] had noticed the rouleaux formation of the clumping red cells and that the sedimentation velocity increased with increase of the aggregation of the red cells. Later, he suggested that this increased aggregation might be due to a new *blood element* which he had observed in freshly examined blood smears. Microscopically, each cell aggregation showed a circular colorless zone in its center, around which the cells clung. This circular zone he has found to be a red cell which has undergone autohemolysis and has acquired this chemotactic-like power to attract other red cells around it and form clumps. He has found the number of these autohemolyzed red cells in direct proportion to the rapidity of the sedimentation. This can be explained by Stokes' law of suspension stability and sedimentation velocity; namely, "the sedimentation velocity of the corpuscle in a suspension of globular elements in fluid is proportionate to the square of their radius." Hence, clumps formed through aggregation of cells will show a quicker sedimentation velocity than isolated cells, and the more numerous these clumps, the more rapid the sedimentation velocity.

Linzenmeier,[7] in his study of the relation of the capillary circulation to blood sedimentation, has observed, that in the capillaries of a healthy individual, a uniform circulation of fine granular bodies is present; whereas, in cases with high fever, or in parturient women, the circulating bodies are coarsely granular and unevenly divided in the blood stream of the capillaries, and there can also be observed a high degree of clumping of the red cells, rouleaux formation and stasis. Can we not, therefore attribute this change in the character of the capillary circulation to these autohemolyzed red cells whose action Fahraeus has observed in freshly examined blood smears?

Höber[8] has shown that erythrocytes wander to the anode and, therefore, carry a negative charge. Schürer and Eimer[9] observed that the corpuscles of healthy individuals wander much more quickly to the anode than in parturient women and inflammatory conditions. The sedimentation velocity has been shown to be associated with a change in the relative proteid compositions of the plasma, i.e., an increase in globulin and a decrease in albumin. Höber[10] states also that different proteids exert different influences on the electrical burden of the corpuscles, i.e., the negative burden is greater in albumin than in globulin solutions. In other words, the negative burden of the corpuscles is diminished and the sedimentation velocity is increased. Linzenmeier has shown that if the plasma is treated with substances which are adsorbents for positive particles, the negative burden of the corpuscles is increased and hence the stability of the blood is raised.

To summarize these findings, we can say that in inflammatory conditions the electrical burden of the cells is diminished, due to an increase of globulin and fibrinogen and resulting in an increased sedimentation. Another factor in the increased S.V., as pointed out by Höber, is that the increased globulin not only diminished the electrical burden of the cells, but, owing to its increased viscosity (the degree of viscosity of proteid solutions being indirectly proportional to their electrical burden), it has also a direct action on the S.V.

It remains to be shown whether the autohemolysis and agglutination of Fahraeus is but an added factor in the process of increased S.V. as is the increased globulin and its increased viscosity. The colloid chemical explanation seems the most plausible. It is interesting to note that Frisch, of Vienna, prior to Fahraeus, had observed the fibrinogen content of the serum to be a very sensitive index of the activity and intensity of an existing tubercular process.

But not only the plasma is responsible for the different S.V. The red cells must also be considered, for the red cells of the horse with its quickly sedimentating blood, hold their speed of sedimentation, partially, when transfered into the plasma of oxen, with their slow sedimentating blood. The difference in the nucleoproteid content of the red cells (34 per cent in horse, 20 per cent in cattle) has been mentioned in explanation of this peculiarity.

CLINICAL VALUE OF THE TEST

The entry of the sedimentation test, like all new procedures in medicine, was heralded with great enthusiasm by many workers,—more so in Europe than in America. And like all new procedures, the enthusiasm it evinced when still in the theoretical and speculative stage, abated somewhat, and became more mature when put through the *acid test* of clinical application. During the past few years, with the intense work done, particularly in Europe, the value of the test from its most useful standpoint; namely, clinical, has been ascertained, and with it came its limitations.

Regarding the sedimentation velocity, we ought never to forget that we are dealing with a phenomenon revealing (as Waugh[11] emphasizes) a *state* or a *condition*, like, for instance, *fever*,—and that this state is just as fre-

quent, or even more frequent, than fever, in pathology. Therefore, it must be understood, that the special value of such a phenomenon is entirely different (it would be unjust to say lower or higher) than the value of such symptoms as eosinophilia, complement fixation, and others, which are characteristic for only one single group of diseases or even for one special disease. The following examples illustrate the point: Given a patient of whom we know nothing other than the presence of an eosinophilia in the blood, will make us suspicious of the presence of one of a group of diseases. Knowing nothing else about the case but that there is no eosinophilia present, this statement will have no value at all, and will seem absurd. If, on the other hand, we know nothing regarding a patient except that he has or has not a fever, the value of these two statements will be about the same, neither one nor the other will promptly help us to make a diagnosis, but both statements will be of general value. From this standpoint it seems false and inconsistent to call fever a symptom, for the translation of the Greek word "symptom" is "accidental finding," which would be the proper term for eosinophilia. For fever, increased sedimentation velocity and similar general phenomena, the expression "state" is undoubtedly a much more corresponding term. (The expression "condition" has been incorporated in the medical terminolgy with a different meaning; namely, "the sum of all outside influences in contradistinction to constitution.")

1. *As an Aid to Diagnosis.*—We find the S.V. increased in all conditions of increased protein catabolism, whenever there are higher products of protein catabolism present or increased in the blood. Consequently, in all febrile conditions; in many inflammatory conditions without fever; in pregnancy after the third month (be it due to increased cholesterol content of the blood or to other physiochemical changes of the serum); after parenteral introduction of a foreign protein; after therapeutic x-ray treatment or influences of radio-active substances upon the organism; in many kidney diseases, due to the presence of certain higher products of protein catabolism in the blood revealing themselves in a rise of a certain fraction of the N.P.N.; in liver diseases where there is a lack of normal protein catabolism present and in tumors where there is resorption of cell products due to disintegration of the tumor. Among other conditions without fever which also show increased S.V. must be mentioned active lues and general paresis and all conditions with decrease of red cells. Runge[12] has noticed an increased S.V. in dementia praecox and only occasionally increased S.V. in melancholia, hysteria, and in psychopathic patients. In arteriosclerosis and in postencephalitis the S.V. was considerably increased.

When considering that in the first years of the Fahraeus test the increased sedimentation velocity has been found in all these mentioned conditions only *successively,* and in the beginning without adequate theoretical foundation, you can imagine the enthusiasm the discovery produced and how much was supposed to be diagnosed from the S.V. The first application of the test to the diagnosis of pregnancy has already failed to keep its promise, for the reaction was only positive with certainty after the third month, and even then, it could be used for differential diagnosis from tumors,

only when there was no disintegration of the questionable tumor, or the presence of an inflammatory condition elsewhere in the body. You see then how restricted here, in reality, is the value of the test.

The attempt to differentiate between appendicitis and adnexitis was, quite obviously, a failure. In the differential diagnosis between inflammatory disease of the adnexa and ectopic pregnancy the sedimentation test is of great value, for in uncomplicated ectopic pregnancy of the first two or three months the sedimentation test will be normal. (If there are slight reactive changes of the peritoneum or intraligamentary hematoma present, it will be slightly increased.) However, all inflammatory diseases of the adnexa show a very rapid S.V. Ruptured ectopic pregnancy will of course be followed by a rapid S.V. In the differentiation of inflammatory and non-inflammatory tumors of the pelvis the test will be of value.

Concerning inflammatory conditions in general, we must say the following: "If we have a case with pain, tenderness, and muscular rigidity in the ileocecal region and with 20,000 leucocytes, we will not need the sedimentation test to make the diagnosis appendicitis, and to differentiate from adnexitis it will be of no help to us. It will, however, give us an index of the severity of the condition and possibly of the prognosis. When we see a child with high temperature and pus in the urine, we do not need the sedimentation test to aid us in the diagnosis." Whether the test will ever be of practical use to confirm the diagnosis of general paresis or to make the diagnosis of congenital lues of the newborn (the blood from the umbilical vein shows very slow S.V. normally and in congenital lues a very rapid S.V.), or to differentiate between real or pseudocroup, we do not know. But the test is of very great value in the diagnosis of all those conditions, where there is a suspicion of a latent or an acute inflammatory process and where the leucocyte count is indefinite and the temperature insignificant. In such cases, increase of the S.V. will give us the doubtless decision of the presence of inflammation, as the following case illustrates:

CASE 1.—D. Y., male, forty-two years old, paper hanger, presented himself at the clinic for examination. For the last few weeks while hanging paper he was unable to raise his hand above his head without causing sharp pain in the right lower abdomen. Otherwise he felt well. He gave no history of previous illness other than an attack of abdominal cramps two months previous, which had lasted only a few hours.

Examination revealed a small indefinite and tender mass in the right lower abdomen. Otherwise negative. W. B. C., 9,100; polys, 78 per cent; temperature, 98.4° F.; blood Wassermann negative. S. V., line No. 12 in twenty-four minutes.

As this revealed the presence of a marked inflammatory condition, a second physical examination was made with the purpose of locating possible foci of infection. The findings were negative. A laparotomy revealed multiple adhesions walling off a ruptured appendiceal abscess.

Alexander[13] emphasizes the value of the test in this latter sense (as many authors do) as a diagnostic check in certain cases of chronic arthritis and joint conditions. In early tuberculosis when the temperature, sputum examination, and x-ray do not show anything definite, the sedimentation test is of great value. A *repeated* normal S.V. rules out the presence of active tuberculosis.

In illustration of the diagnostic value of the test we desire to quote only two cases in which the reaction has aided us in the laboratory of the Barnert Hospital. (Becker, of Washington, D. C., who carried out many of the tests will publish them in detail.)

CASE 2.—M. R., aged eleven, was a very nervous child. She complained of pain in her back without characteristic symptoms. W. B. C., 13,000; polys, 75 per cent; temperature normal. S. V. line No. 12 in twenty-seven minutes. On account of S. V. we suspected tuberculosis of the spine, and this was confirmed several weeks later. The earlier x-ray did not reveal any disease.

CASE 3.—H. L., aged twenty-two, a student, complained of tiredness, general malaise, inability to concentrate, and a feeling of being "off color," which had lasted three weeks. He feared the presence of a latent infection. There was no loss of weight. Physical examination was negative. Temperature was normal, W. B. C., 6,800; polys, 63 per cent; lymphocytes, 25 per cent (21 per cent small, 4 per cent large); eos, 2 per cent; R. B. C., 4,400,000; Hb., 84 per cent. Urine was negative, and Wassermann was negative.

Provisional diagnosis, neurasthenia.

S. V., 68 minutes to line No. 12. From the latter we concluded the presence of a latent infection either with or without neurasthenia, and advised x-ray of the teeth and sinuses. X-ray revealed large apical abscess of right upper molar.

Two weeks following extraction of the tooth, the S. V. was 122 minutes to line No. 12 and patient felt greatly improved.

Friedlaender (and many others) recommend the test as an index of operability in chronic diseases of the adnexa and chronic perityphlitic abscesses. "The operation is to take place only when the blood sedimentation has reached normal values." This is considered as an indication that the inflammatory process is completely encapsulated. In such conditions (following Friedlaender and others) the S.V. is of much greater value than leucocyte count and temperature. (Concerning all the details of this question we desire to refer again to Friedlaender's paper.)

A negative test, of course (as always in medicine), should be used with caution and as an added check. A *repeated* negative Fahraeus, however, is very instructive, for it rules out the presence of an active or latent inflammatory or degenerative process. As a positive result is always found in conditions where there is an increase of leucocytes, the test can be used with absolute reliability in place of the leucocyte count at the bedside, or where a microscope is not within reach.

Generally speaking, the diagnostic value of the test is only a restricted one. Its chief value is its being an extraordinarily fine reagent, indicating intensity, activity, and (when repeated several times) the course and prognosis of the disease.

From a mathematical consideration, the variations of this test are much greater than those of the blood count. If, for instance, we take 7,000 leucocytes as normal and 21,000 as a high leucocytosis, the ratio of these two values is 1/3. In the sedimentation test the normal value of sedimentation down to line No. 12 is about 130 minutes. In acute inflammatory conditions we very frequently find values of nine to thirteen minutes. Here we have a ratio of 1/10 and 1/15, respectively. Of course, the greater variation is not the only moment in favor of the test. Clinical observation, especially

in tuberculosis of the lungs, has shown the reaction to be a very sensitive one as well. This combination of greater variations *and* relatively high sensitiveness, makes the reaction a very valuable one, especially concerning the course and the prognosis of chronic inflammatory conditions.

2. *As an Aid to Prognosis.*—We have found the test to be a valuable aid in the prognosis of acute inflammatory conditions, preoperative and postoperative, and in chronic conditions such as tuberculosis and chronic lung abscess. Especially in chronic pulmonary tuberculosis has it proved to be a definite index of the lung process. With the lessening of the catabolic process by increased fibrosis, there results a corresponding decrease in the absorption of catabolic products which is sensitively manifested by a resulting decrease in the sedimentation velocity, until it approaches an apparently normal ratio (S.R. 13/13), i.e., line No. 12 in 130 minutes or over. At this stage, in the absence of positive clinical findings, we can safely say that the patient is ready for discharge.

The sedimentation test is of greatest value as an added check to temperature, weight, and physical findings in a suspected case of early incipient apicitis, for, in the diagnosis of apicitis, the leucocyte count is insignificant, the sputum usually negative, and the x-ray is not able to reveal anything regarding the *activity* of the process. If we see a patient for the first time and consider his statements concerning fever and loss of weight unreliable, and if the physical findings are not decisive, the S.V. is the only *objective* statement to help us in our diagnosis; and, the test is considered today (following the research of Westergren,[14] of Sweden, Frisch and Starlinger,[15] in Vienna, and others) as the most sensitive index of the course of the disease, value of the prescribed therapy, prognosis, and fitness of a patient for discharge from the sanatorium.

In Austria, the test has been introduced as a routine examination in all the larger tuberculosis sanatoria and is considered of major importance as an added check to temperature, weight, and physical findings. When a patient is discharged, he is instructed to take his temperature and weigh himself regularly, and to return to the clinic at definite intervals for a S.V. test. *Here we see the blood sedimentation test playing exactly the same rôle concerning the course of a chronic tuberculosis, as the complement-fixation test in the course of lues.* (One of us, H. W., has been able to appreciate the value of this procedure personally, while working in a tuberculosis station, in Vienna, during the past year.)

The following case of postpneumonic lung abscess illustrates the marked degree of variation of the S.V. as compared to that of other laboratory methods and its usefulness from the viewpoint of prognosis.

CASE 4.—B. L. S., aged forty-eight, male, white, a printer. He was discharged May 25, 1924, with diagnosis of chronic lung abscess following unresolved pneumonia. The diagnosis was corroborated by the x-ray. At the time when the patient was running a septic temperature between 99° and 103° F., the leucocyte count was 17,200, and the S. V. twelve minutes to line No. 12.

On June 25, 1924, one month after discharge, the patient returned to the clinic after coughing up a large amount of pus. Temperature, normal; leucocyte count, 11,000; S. V.,

sixteen minutes to line No. 12, still indicating the presence of an active condition as also shown by the x-ray.

August 13, 1924, the patient returned from the mountains in greatly improved condition. Temperature was normal, and leucocyte count, 10,000. The S. V. had changed from sixteen minutes to ninety-four minutes.

In acute inflammatory conditions we have found, that where the S.V. is less than ten minutes to line No. 12 (S.R. under 1/13), the prognosis is always poor. This is most marked in pneumonia, empyema, lung abscess, puerperal septicemia, and peritonitis.

In postoperative cases the S.V. shows a gradual return to normal. Should it rise again we are at once warned of an impending complication such as wound infection, peritonitis, or pneumonia. The S.V. in postoperative pneumonia is usually very rapid. Should it be under ten minutes the prognosis is poor.

The following case illustrates this:

CASE 5.—Miss R. G., a saleslady, aged thirty-nine, was admitted July 23, 1924, with diagnosis of chronic cholecystitis. She was operated on next day and an enlarged and thickened gall bladder containing several stones, was removed. On the third day postoperative the temperature rose to 104.3° F.

Examination showed extensive area of consolidation involving lower ⅔ of left axilla and extending to the back. Fetid odor of the breath developed.

Diagnosis of lung abscess confirmed by x-ray August 5, 1924. W. B. C., 18,000; S. V., nine minutes to line No. 12.

Patient died Aug. 6, 1924.

It would seem that the sedimentation test is not only an index of the degree of absorption of catabolic products, but is also an index of the degree of resistance of the host and the virulence of the organism. Else, why should the S.V. be less in empyema, pneumonia, and in caseous tuberculosis, than in septicemia, for instance, where the amount of protein catabolism and absorption in the latter is manifestly much less? Furthermore, in two cases of lobar pneumonia with equal lung involvement, we find one has a S.V. of twenty-two minutes whereas the other has a S.V. of nine minutes. Both have apparently the same areas of absorption, yet the latter dies and we attribute death to a lessened resistance of the host and an increased virulence of the organism. All other factors being equal, the rate of sedimentation seems to correspond *more* to the type of organism and the resistance of the patient, than to the degree of catabolism and protein absorption.

CONCLUSION

In conclusion, we wish to emphasize the value of the sedimentation test in tuberculosis of the lung. Concerning the other possibilities of the test, in medicine and in surgery, the enthusiasm of the first years is subsiding here, as it has in Europe, but in many conditions other than tuberculosis, the sedimentation test has proved its value, and therefore justifies its adoption as an added check to leucocyte count and temperature, subjective and objective findings, and in the diagnosis, course, and prognosis of acute and chronic inflammatory conditions.

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COD-LIVER OIL TREATED WITH MAGNESIUM HYDROXIDE IN THE TREATMENT OF SURGICAL TUBERCULOSIS*

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THE methods which are at the present time available for the treatment of tuberculous abscesses are at the best unsatisfactory or difficult of application in certain cases. Excision is not always possible, incision and drainage results in secondary infection, and aspiration alone is not always curative.

The alternative would seem to be a method which would combine aspiration with the injection of some material possessing an inhibitory or direct antiseptic action on the tubercle bacillus. Such a solution should be very slowly absorbed from the abscess cavity, nonirritating and nontoxic.

During the past two years we have carried out a series of experiments at the Cincinnati Tuberculosis Sanitarium with the object of developing a medium which will have a curative action on closed tuberculous abscesses. Several solutions have been tried, some with no success, others with encouraging results.

In all these experiments it was determined by tests and guinea pig inoculations that the tubercle bacillus was always present and was the sole organism to be demonstrated.

In the course of our work it became apparent that the best medium was a heavy oil which would be slowly absorbed. We decided upon cod-liver oil, basing our choice upon its beneficial effects in general tuberculosis when administered by mouth. Our choice of cod-liver oil was subsequently justified by the recent work of Campbell and Kiefer,[1] who found that it exhibits a definite inhibitory and bactericidal effect on virulent strains of tubercle bacilli.

Cod-liver oil, when injected into tissues unmodified, is too acid to be tolerated, and must be neutralized or alkalinized in order to be safely injected. After trials with various alkalis we determined upon magnesium hydroxide. Equal quantities of magnesium hydroxide and commercial cod-liver oil were boiled together and then centrifuged. We expected a soap to form, but, to our surprise, found that the cod-liver oil was supernatant, unchanged in appearance, and recovered in almost the same amount as when introduced. This oil, however, is alkaline to methyl red and alcoholic phenolphthalein. We have tested it several days after this treatment and found it still alkaline. In this alkaline form the use of cod-liver oil in an abscess cavity is nonirritating and safe.

In our work we have used a commercial milk of magnesia put out by

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one of the well-known drug houses, as it is a suspension of magnesium hydroxide in water. Theoretically, a cold-pressed cod-liver oil would have more antiseptic value, but we have used an ordinary commercial product.

During the last five or six months we have applied this method of treatment with uniform success to the various tuberculous abscesses we have encountered at the sanitarium and elsewhere.

Our success with this solution received an unexpected explanation when the work of Kugelmass and McQuarrie[2] was recently published. These observers have found that cod-liver oil possesses in itself the property of emanating ultraviolet rays. As these are the rays upon which we depend for our results in heliotherapy and quartz lamp treatment of tuberculosis it

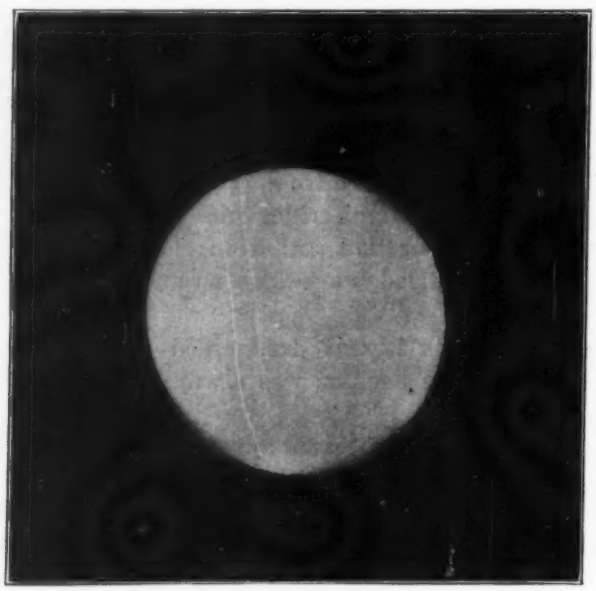

Fig. 1.—Film taken by normal cod-liver oil.

would seem that we are placing in an abscess cavity an agent constantly emanating rays of known curative properties. That these rays are of no small intensity is shown by the accompanying film, showing the result of forty-eight hours exposure to cod-liver oil. This film was obtained by inserting an enameled metal dish three-quarters full of cod-liver oil under an x-ray film in its original envelope. The envelope was closed and placed in a lead-lined cabinet for forty-eight hours, when the film was developed. In order to determine whether the treatment of the cod-liver oil with magnesium hydroxide had any effect on the power of emanation, a second similar experiment was performed with the oil so prepared. This film, Fig. 2, shows that here is some slight loss in power of emanation.

It has been stated that the rays responsible for this action upon the photographic plate are ultraviolet, but in none of the published reports have I been able to find any competent physical research to substantiate this belief.

It has also been alleged that the action upon the photographic film is entirely chemical, due to vapor emanating from the oil.

Some preliminary experiments have therefore been carried out, with the assistance and under the direction of Gowdy, of the Physics Department, University of Cincinnati. We have established the following facts: that we have here a substance emitting definite rays. These rays are probably not of one type, but made up of rays of various wave lengths. These rays will not penetrate glass or fusible quartz. They will penetrate paper to a slight degree. Placed in an ionizing chamber the oil shows definite but slight ionizing power. Enclosed in a sealed fusible quartz flask no ionization is obtained.

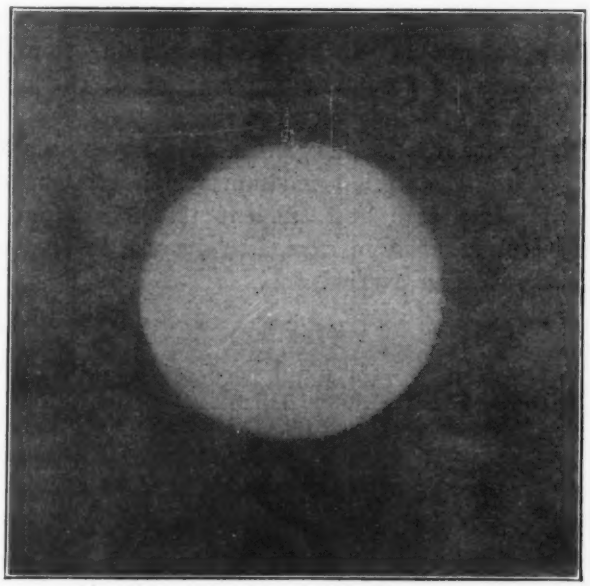

Fig. 2.—Film taken by cod-liver oil after treatment with magnesium hydroxide, showing slight absorption of emanation.

The ionizing power of cod-liver oil is not increased by exposure to a mercury quartz lamp.

That the photographic effect is not due to vapor we believe we have determined by directing a current of air upon an x-ray film placed in a light-tight chamber. This current of air has been forced through cod-liver oil by suction. The experiment was continued for forty-eight hours, at the end of which time no effect was noticed upon the developed film.

The density of the photographic picture varies with the mass of the oil and is not a surface effect. For the same surface, denser shadows are produced by greater quantities of oil.

It is interesting to note that Hess in his work on olive oil in rickets has found that when it has been exposed to the mercury quartz lamp the oil acquires a fishy odor, like cod-liver oil.

The physical problem of the exact nature of the rays is not a simple affair and is still under investigation.

The injection of this alkalinized oil into normal tissues has been shown to be harmless and without any irritative or inflammatory sequelae. Rabbits into whose pleural cavities seven and eight cubic centimeters of the fluid have been injected have behaved normally following the injection and when sacrificed ten days after the injection no lesions, macroscopic or microscopic, have been noticed in the pleurae.

We, therefore, believe that the injection of this fluid in a normal pleura is a safe and harmless procedure and by analogy the same would apply to any serous cavity.

Technic.—The skin overlying the abscess and surrounding area is sterilized, and pus aspirated by a long needle or trocar with a caliber sufficiently large to allow of complete emptying of the cavity. It is important to withdraw all of the pus. The abscess is never entered directly, the needle being introduced through at least two inches of surrounding tissue. The amount of pus withdrawn is noted and an equal amount of the oil is introduced through the needle which has not been removed.

To summarize our results in this preliminary report, we believe that we have in alkalinized cod-liver oil a medium which rests upon clinical and theoretical grounds as a safe and efficient treatment for closed surgical tuberculosis. We feel justified in extending its use to empyema, and work along that line is now being carried on.

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A STUDY OF THE STABILITY OF SOME OF THE CONSTITUENTS OF THE BLOOD IN THE TUBERCULOUS*

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FOLLOWING the confirmation of the usefulness of Matefy's reaction for the determination of the activity of a tuberculous process by Kromeke[1] it has been the subject of some experimental work and clinical application in this intsitution for a period of several months.

The technic as originally set forth consisted in the preparation of a fresh 0.5 per thousand solution of aluminum sulphate from a 0.5 per cent stock solution. Of this reagent, 1 c.c. was added to 0.2 c.c. of the serum under test. The tube was well shaken and then set aside for an hour and a half at room temperature after which readings were made; distinct flocculation (not mere turbidity) indicating a positive reaction. In our preliminary studies of this reaction it was at once observed that positive results were being obtained with the blood sera from active cases of tuberculosis and that in individuals giving positive flocculation reactions active tuberculous disease was evident in a high percentage of the number.

Using the technic as outlined above, a series of experiments were made to determine the optimum temperature at which the reaction occurred. Observations were made at three different temperatures; namely, 10° C., 20° C., and 37° C. In working with sera from tuberculous and nontuberculous individuals, it was at once apparent that this reaction is seldom encountered at the lowest temperature even with known reacting sera.

Table I

TUBERCULOUS				NONTUBERCULOUS			
PATIENT	10° C.	20° C.	37° C.	PATIENT	10° C.	20° C.	37° C.
508	−	+	+	R-I	−	−	−
504	−	+	+	R-II	−	−	−
549	+	+	+	386	−	−	−
385	−	+	+	388	−	−	−
408	−	+	+	410	−	−	−
406	±	+	+	10E	−	−	±
550	−	−	+	20E	−	−	− (Luetic)
495	+	+	+	30E	−	−	−
				40E	+	+	+ (Luetic)
				50E	−	−	±
				60E	+	+	+ (Luetic)
				489	−	−	−

At 20° C. and at 37° C., the results are quite parallel, so that it was considered that 20° C. would constitute a satisfactory working temperature for further experiment.

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Considering the amphoteric properties of proteins in solution, by virtue of their amino-acid structure, another project was undertaken to determine the effect of a varying P_H concentration of the flocculating reagent. Diluents with an established P_H concentration of 6.3, 7.0, 7.4, and 8.0 were used in preparing the aluminum sulphate solution. These were then used with known reacting and nonreacting blood sera. As a result it was noted that an acidity or an alkalinity seemed to greatly interfere with the reaction and that for best results the strict neutrality of freshly distilled water (P_H 7.0) was desirable.

In the report of Loeb[2] it is stated that slight concentrations of neutral salts will so affect the potential difference (P.D.) of the electrical double layer surrounding suspended solid aggregates (micelles) that a critical limit may be reached, so that the particles thus altered in their immediate environment will coalesce upon colliding and rapidly settle. In the case of true solutions of proteins, i.e., where the ultimate unit in solution is the protein ion or protein molecule, greater concentrations of neutral salts are necessary to effect flocculation. With this thought in mind another series of experiments was made wherein varying concentrations of the precipitating reagent (aluminum sulphate) were used, as follows: 0.1 per cent, 0.075 per cent, 0.05 per cent, 0.0375 per cent and 0.025 per cent. Upon applying the reaction with these varied concentrations of the reagent to a number of sera from tuberculous and nontuberculous cases it was at once apparent that in dilutions greater than 0.05 per cent the reaction was not obtained irrespective of whether or not the blood serum was from a tuberculous individual. On the other hand, concentrations of the salt greater than 0.05 per cent gave reactions of varied intensity quite regularly with all classes of blood sera.

To summarize the results, it was apparent that the optimum concentration, for clearly defined yet reliable reactions was probably at the 0.05

TABLE II

TUBERCULOUS PATIENTS	CONCENTRATION ALUMINUM SULPHATE %					NONTUBERCULOUS PATIENTS	CONCENTRATION ALUMINUM SULPHATE %				
	0.1	0.075	0.05	0.0375	0.025		0.1	0.075	0.05	0.0375	0.025
487	+	+	+	−	−	501 (leutic)	+	+	+	−	−
484	+	+	−	−	−	413	+	+	−	−	−
486	+	+	+	−	−	411	+	−	−	−	−
358	+	±	−	−	−	515	+	±	−	−	−
499	+	+	±	−	−	EN	+	±	−	−	−
531	+	±	−	−	−	398	+	±	−	−	−
280	+	+	+	−	−	414	+	+	−	−	−
						412	+	+	−	−	−
						10e	+	+	−	−	−
						20e (leutic)	+	+	−	−	−
						30e	+	+	−	−	−
						40e (leutic)	+	+	+	−	−
						50e	+	+	+	−	−
						60e (leutic)	+	+	+	−	−

per cent concentration point. This observation was clearly in accord with the original report covering the technic of the reaction.

Thinking that the length of the incubation period prior to readings might affect the final result and in that way have a bearing on the usefulness of the test, a group of sera from tuberculous and nontuberculous individuals were subjected to the test and readings made at thirty-minute intervals for a period of two hours.

TABLE III

TUBERCULOUS PATIENTS	INCUBATION PERIOD—HR.				NONTUBERCULOUS PATIENTS	INCUBATION PERIOD—HR.			
	½	1	1½	2		½	1	1½	2
385	−	−	+	+	R-1	−	−	−	−
508	−	−	+	+	R-2	−	−	−	−
504	−	±	+	+	10e	−	−	−	+
549	+	+	+	+	20e (leutic)	−	−	−	−
493	−	+	+	+	30e	−	−	−	−
550	−	−	±	+	40e (luetic)	−	−	+	+
219	−	+	+	+	50e	−	−	−	±
220	−	−	+	+	60e (leutic)	−	+	+	+
38	−	−	+	+	541	−	−	−	−
72	−	+	+	+	526	−	−	−	−
63	−	+	+	+	489	−	−	−	−
46	−	+	+	+	161	−	−	−	−
31	−	+	+	+	30	−	−	−	±
54	+	+	+	+	42	−	−	−	−
253	−	+	+	+	72	−	−	−	−
48	−	+	+	+	35	−	−	−	−
182	−	+	+	+					
144	−	+	+	+					
20	−	+	+	+					

While the reaction was observed with most sera from tuberculous individuals in a period of one hours' incubation yet there were a number of known reacting sera that failed to give the reaction at any point prior to an hour and a half of incubation. At two hours incubation distinct flocculation occurred in many of the tubes containing sera from nontuberculous individuals. From these observations it was decided that an incubation period of one and one-half hours at room temperature (20° C.) would constitute the optimum.

In the light of these preliminary findings the test was instituted as a regular procedure upon the admission of patients to the hospital, using 0.2 c.c. of the serum, unheated, the tests all being made on the day following the taking of the specimen. To the serum 1 c.c. of 0.05 per cent solution of aluminum sulphate (C.P. salt dissolved in freshly distilled water) was added, the tube well shaken, set aside at room temperature (20° C.) for an hour and a half at which time readings were made. Distinct flocculation with settling and clearing of the supernatant fluid constituted a positive reaction. Only a few borderline reactions occur; in the great majority of instances the reaction is clear cut and well defined. Heating of the blood serum to 56° C. for fifteen to thirty minutes, the usual procedure of inactivation, interferes greatly with the reaction, almost to the point of complete inhibition.

Up to date, 300 examinations have been made in which clinical findings are available. The results may be classified as follows:

Positive reactions. "Colloid" instability	193	
Of the above, patients clinically tuberculous, with B. tuberculosis present in the sputum	174,	or 90.1%
Patients with clinical diagnosis of active pulmonary tuberculosis. B. tuberculosis not demonstrable in the sputum	14,	or 7.3%
Patients considered to be nontuberculous upon physical examination	5,	or 2.6%
Negative reactions. "Colloid" stability	107	
Of the above, patients clinically tuberculous with B. tuberculosis present in the sputum	42	
Cases with varied diagnoses. B. tuberculosis not demonstrable in the sputum	65	

It is quite apparent that many well-defined cases of pulmonary tuberculosis do not exhibit this reaction property, at least so far as one examination is concerned. Limited observations would indicate that the reaction is not necessarily constant, but may vary from time to time. Further investigation in this respect is indicated. The problem has been attacked with the object of determining the incidence of tuberculous disease in individuals giving the reaction of "colloid" instability. Thus far, of the 193 patients giving a positive "colloid" reaction only 5, or 2.6 per cent, have been discharged as being nontuberculous. One of these patients was a diabetic with well-established condition of ketosis and at the time of the test had a fasting blood-sugar content of 440 mg. per 100 c.c. of blood. Under dietary treatment and insulin administration over a period of two months the blood sugar was reduced to 222 mg. per 100 c.c. of blood at which time the "colloid" stability reaction was negative. It is thought that the ketosis may have been responsible for the flocculation in the original reaction.

It is our experience that the "colloid" instability reaction is observed in the blood sera of the tuberculous in many cases and is very probably in accord with the often reported finding that the globulins are increased in amount in the blood stream of the tuberculous.

In our group of nontuberculous individuals it was noted that two of the three syphilitic cases gave a positive reaction. This test cannot be considered as being specific for tuberculosis, but may be of value in the diagnosis of tuberculosis when other diseases can be excluded.

I am grateful for the assistance received from clinicians of this hospital in securing clinical data.

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STUDIES OF THE COLLOIDAL GOLD REACTION USING GOLD PREPARED BY AN ELECTRICAL METHOD*

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PREVIOUS descriptions of the colloidal gold reaction have been based either upon the preparation of the gold as originally described by Lange,[1] or modifications of his method.[2, 3, 4, 5, 6, 7] The present paper reports a series of spinal fluid examinations in which colloidal gold prepared by an electrical method was employed.[8]

The method of preparing the gold sol is as follows: The apparatus (Fig. 1) consists of a coil of five hundred feet of number eighteen gauge asbestos covered wire (A), wound on an iron pipe one inch in diameter and one-eighth of an inch thick. Five one hundred watt lamps (B) connected in parallel are used as resistance. One wire leads from the source of the current supply through the lamps into the coil; the other end of the coil is connected to one of the gold electrodes (C). These electrodes are four inches in length, of number eighteen gauge, 100 per cent pure gold wire.† The second electrode is connected to the other pole of the current source.

Preparation of the solution.—Two hundred c.c. of hydrochloric acid solution are made by adding two drops of normal hydrochloric acid to 200 c.c. of distilled water. This gives a solution to about N/10,000. A clean Pyrex beaker may be used to best advantage. The electrodes are immersed in this solution, and steady sparking is allowed to take place for two and one-half minutes.

Stir the solution well and allow to stand overnight; decant, and it is ready for use.

The solution must be stored in Pyrex or nonsol glass-stoppered flasks, and the tubes used in the test should be of the same type of glass.

As is well known, certain precautions should be observed in performing the test in order to exclude errors in technic. Glassware is not to be used for any other purpose, and should be cleaned with aqua regia, then thoroughly washed and rewashed with distilled water. The electrically prepared gold must have a color comparable with a solution of cobalt nitrate-potassium dichromate described by Lee.[9] Its reducing power should be such that the addition of 1.7 c.c. of a freshly prepared 1 per cent sodium chloride solution causes a reduction to a blue color within one hour, and complete reduction (colorless) in twenty-four hours. The gold solution should not be reduced by a normal spinal fluid, while a typical reduction curve should be given by a tabetic spinal fluid. It is essential that the spinal fluid be examined for the presence of blood (using the benzidine method) inasmuch as we have found

*From the Pathological Laboratory of the Lenox Hill Hospital, New York.

†This wire may be obtained from Handy and Harmon, Fulton and Gold St., New York City.

that when blood or blood serum is added to normal spinal fluid a false reduction is obtained. A similar observation was made by Kellert.[10]

The reactions obtained with the use of this gold are recorded as described in "Laboratory Technic, the Methods Employed at St. Luke's Hospital";[9] and for the information of those not familiar with this scale, the following table is given.

COLOR	NUMERICAL COLOR VALUE
Colorless	7
Pale Blue	6
Steel Blue	5
Blue	4
Blue Violet / Violet Blue	3
Violet Blue Red / Red Blue	2
Violet Red / Red Violet	1
Red	0

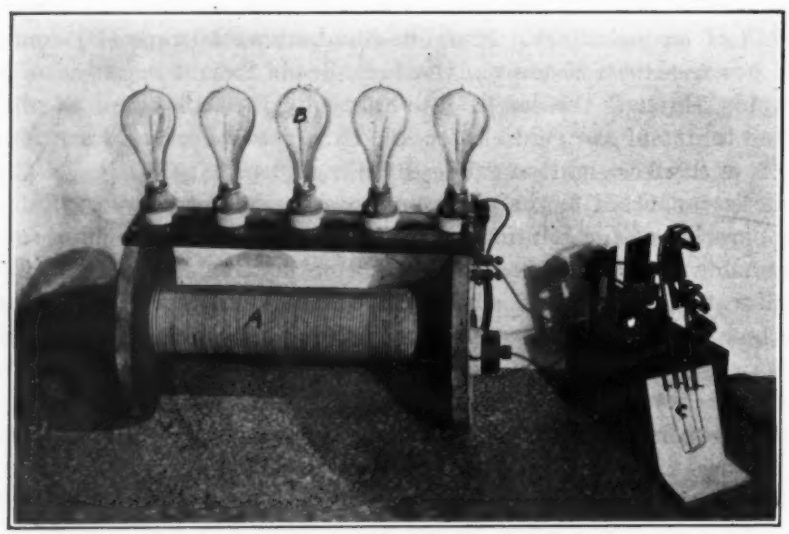

Fig. 1.

Syphilis.—In the twenty-six cases of syphilis (Table I), seven gave a negative curve, a negative Noguchi globulin, and a negative spinal fluid Wassermann. In five of these the blood Wassermann was positive, and in one instance the cell count was 10, no cells being found in the others. Two cases had a negative blood Wassermann. None of these seven cases was diagnosed clinically as syphilis of the central nervous system. Of the nineteen spinal fluids giving curves in the luetic zone, twelve were from cases definitely diagnosed as syphilis of the central nervous system. In nine of these, the spinal fluid Wassermanns were positive, and in seven of these nine, the blood Wassermann coincided. The blood Wassermann was not done in the other two cases. The remaining seven cases of this group giving a luetic curve were all diagnosed as having various forms of syphilis though without clinical signs of cerebrospinal involvement. In these cases the spinal fluid Wassermann was positive

in two instances, while the blood Wassermann was positive in six, not being done in the other case.

When a reduction of the gold in the luetic zone is obtained in cases of syphilis involving other organs than those of the central nervous system, the

TABLE I

SYPHILIS

HISTORY NO.	CELL COUNT	GLOBULIN	WASSERMANN		GOLD CURVE	DIAGNOSIS
			SPINAL FLUID	BLOOD		
1394	0	0	0	4+A 4+C	0000000000	Tertiary syphilis
1437	0	0	0	0	0000000000	Syphilis. Chronic nephritis. Autopsy
1387	0	0	0	2+A 3–4+C	0000000000	Subacute endocarditis Right hemiplegia
2083	200	2+	10+A 10+C	4+A 4+C	7777642100	Cerebrospinal syphilis
2466	10	0	–	4+A 4+C	0000000000	Chronic endocarditis Luetic aortitis
2719	90	±	3+A 8+C	2+A 4+C	7773221000	Tabes
2853	20	+	8+A 9+C	4+A 2+C	7777730000	Cerebrospinal syphilis
2995	60	±	0	4+A 2+C	3576631000	Cerebrospinal syphilis
–	140	+	8+A 8+C	–	7774000000	Cerebrospinal syphilis
K	–	–	4+A 8+C	4+A 4+C	2277742410	Cerebrospinal syphilis
5984	220	+	10+A 10+C	4+A 4+C	1127743210	Cerebrospinal syphilis
3223	28	+	10+A 10+C	–	7777765330	Cerebrospinal syphilis
P315	12	+	–	–	7752201230	Cerebrospinal syphilis 5/1/23
P315	30	+	0	–	7774440000	1/2/24
3169	23	0	0	4+A 4+C	7777777522	Secondary syphilis
3244	10	0	0	4+A 4+C	1776520000	Congenital syphilis
3352	0	0	0	4+A 4+C	0000000000	Chronic endocarditis Syphilis of aorta
2213	6	0	0	0	4777744000	Syphilis of central nervous system. Ophthalmic lues
4550	0	0	0	4+A 4+C	0000000000	Tertiary syphilis
4770	0	0	0	4+A 3+C	0357410000	Chronic valvular endocarditis and syphilis
4875	60	3+	8+A 10+C	4+A 4+C	7777743221	Dementia paralytica
5027	8	0	7+A 6+C	4+A 2+C	2236541100	Subacute endocarditis and syphilis
5141	5	0	7+A 5+C	4+A 4+C	2227743111	Dementia paralytica
5216	0	0	0	4+A 4+C	7776542100	Tertiary syphilis
5445	0	0	0	4+A 4+C	0677432111	Facial palsy syphilis
5614	5	0	3+A 3+C	–	7777642110	Tertiary syphilis
2623	0	0	0	0	0000000000	Syphilis—has had treatment

possibility of involvement of the central nervous system must be constantly kept in mind regardless of the cell count, globulin, and the spinal fluid Wassermann. Our experiences in this respect are in accord with those of other authors.[3, 4, 11, 12, 13, 14]

TABLE II

MENINGITIS

HISTORY NO.	CELL COUNT	GLOBULIN	WASSERMANN		GOLD CURVE	DIAGNOSIS
			SPINAL FLUID	BLOOD		
1383	2800	4+	–	–	7777550000	Meningococcus meningitis 5/14/23
1383	5000	4+	–	–	0122773300	5/16/23. After injection of meningococcus serum. Died
1905	270	2+	0	–	1117765220	Tuberculous meningitis. Autopsy
2624	170	+	0	0	11237641000	Tuberculous meningitis. Autopsy
4379	375	2+	–	–	00017774311	Pneumonia—Died Meningitis complication
5100	55	2+	0	0	0017774321	Tuberculous meningitis
3653	400	+	0	0	0000000000	Pneumococcus meningitis Pneumococcus septicemia. Died
6003	2600	4+	–	–	6777777421	Pneumococcus meningitis Pneumococcus septicemia. Autopsy
5392	1300	2+	0	–	0027774321	Tuberculous meningitis 6/21/24
5392	80	4+	–	–	0123776442	6/24/24
3598	130	+	0	–	0000000000	Tuberculous meningitis
5168	155	2+	–	0	7777732100	Tuberculous meningitis 6/3/24
5168	100	2+	–	–	0137743211	6/5/24
5168	160	2+	–	–	0017764311	6/7/24 Died

TABLE III

ENCEPHALITIS

HISTORY NO.	CELL COUNT	GLOBULIN	WASSERMANN		GOLD CURVE	DIAGNOSIS
			SPINAL FLUID	BLOOD		
2938	150	0	0	–	2753200000	Acute anterior poliomyelitis. Autopsy
4744	35	3+	0	2+A 1+2+C	2337776531	Acute suppurative polioencephalitis
5499	0	0	0	0	1137521000	Chronic polioencephalitis
5362	0	0	0	–	0076532100	Chronic superior polioencephalitis
2871	30	0	0	0	2774410000	Acute inferior polioencephalitis 10/11/23
2871	10	+	–	–	346541000	Improved 10/26/23
2871	5	0	0	–	0017761000	11/22/23
5013	9	0	0	0	1127653200	Encephalitis lethargica

TABLE IV

CHOREA

HISTORY NO.	CELL COUNT	GLOBULIN	WASSERMANN		GOLD CURVE	DIAGNOSIS
			SPINAL FLUID	BLOOD		
4116	0	0	0	0	0114555500	Chorea, chronic endocarditis
–	0	0	0	0	0000000000	Chorea
Sch.	0	0	0	0	0000000000	Chorea
4995	0	0	0	0	0000000000	Chorea
1208	10	0	0	0	0000000000	Chorea
4651	0	0	0	0	1266444430	Chorea, chronic endocarditis

A study of Table I shows that there does not seem to be any relationship between the cell count and the gold reaction. This is best demonstrated in a comparison of Case 2083 with a cell count of 200 and a very definite luetic curve, with Case 2853, having a cell count of 20 and exactly the same type and intensity of curve.

Meningitis.—In ten cases of meningitis (Table II), six tuberculous, three pneumococcus, and one meningococcus, all but two gave curves the average

TABLE V

MISCELLANEOUS GROUP

HISTORY NO.	CELL COUNT	GLOBULIN	WASSERMANN		GOLD CURVE	DIAGNOSIS
			SPINAL FLUID	BLOOD		
1174	2	0	–	2+A 2+C	7774400000	Acute gastritis
1721	10	0	–	–	0000000000	Hemorrhage into cerebrum
3516	12	0	0	0	0000000000	Hemorrhage into cerebrum
3986	28	+	0	0	5777410000	Hemorrhage into cerebrum Edema of lungs
832	10	0	0	0	0000000000	Hemorrhage into cerebrum Hemiplegia
4580	10	2+	0	0	0137775420	Hemorrhage into medulla
2357	5	0	0	0	0012000000	Secondary mastoid operation
1931	0	0	0	–	5577653331	Carcinoma of lung Meningeal metastasis
2138	0	0	0	0	0042100000	Idiopathic epilepsy
2318	10	0	0	0	0000000000	Carcinoma of breast
2389	0	0	0	0	0000000000	Glioma of brain. Autopsy
1724	5	0	0	0	0000000000	Carcinoma hypophysis Metastasis choroidplexus
–	45	+	0	0	7765221000	Migraine
2813	0	0	0	0	0000000000	Chronic synovitis of both knee joints
2902	18	0	0	0	1651510000	Carbon monoxide poisoning
P415	0	0	0	0	0000000000	Influenza
3113	0	0	0	0	3765310000	Acute miliary tuberculosis Autopsy
3372	0	0	0	0	0000000000	Bronchopneumonia
1637	8	0	0	0	7410000000	Hyperthyroidism
3504	0	0	0	0	0000000000	Peritoneal adhesions
3815	0	0	0	0	7650000000	Microcephalus malnutrition
3894	0	0	0	0	7533100000	Rickets
3950	0	0	0	0	0000000000	Chronic nephritis Hemiplegia
4170	5	0	0	0	0000000000	Epilepsy
468	0	0	0	0	0003221000	Cerebro arterial sclerosis
4265	0	0	0	0	0000000000	Cataract
4376	12	+	0	0	0000000000	Left sciatic Neuritis
4568	0	0	0	0	0000000000	Chronic myocarditis Hemiplegia
4627	0	0	0	0	1274322000	Typhoid
4618	0	0	0	0	0027543111	Liver abscess Ovarian abscess
4853	0	0	0	0	0000000000	Traumatic neurosis
892	2	0	0	2+A 4+C	0127431000	Chronic suppur. pleurisy
5048	0	0	0	0	0000000000	Syringomyelia
3808	2	0	0	0	0000000000	Chronic nephritis
Br.	0	0	0	0	0000000000	Migraine
5004	0	0	0	0	0000000000	Serous pleurisy
5173	0	0	0	0	0000000000	Multiple burns
5616	5	2+	0	0	7777765333	Acute gastritis

of which shows the peak (maximum reduction) to be at the center (Tube 5). This type of curve does not exactly coincide with the so-called typical meningitic curve in which the peak occurs at the right of the midline (Tube 6-10). The two cases with negative gold curves had positive globulins and cell counts of 400 and 130 respectively.

Encephalitis.—In the six cases of encephalitis (Table III) all gave a reduction, but no specific curve was obtained. The average for the group showed the peak to be in the luetic zone,[15] but the general type of curve was similar to those obtained in meningitis.

Chorea.—There were six spinal fluids examined from cases of chorea, of which four were negative (no curve) and two gave a reduction. In all these cases the globulin was negative, and in all but one, no cells were found. In Case 1208, there was a cell count of ten and a negative curve.

Miscellaneous Group.—Of the thirty-eight cases studied in this group, twenty-one gave no gold reduction. Two cases of acute gastritis and one case of migraine, with a cell count of 40 and a positive globulin, gave curves in the luetic zone. The other fourteen cases did not give any specific type of curve.[16]

Occasionally a gold curve is obtained when all the other findings, both laboratory and clinical are negative; and under these circumstances when the type of curve is not specific for any given condition, we believe that little importance should be attached to the result.

CONCLUSIONS

1. The colloidal gold reaction in which the gold was prepared by an electrical method was studied in eighty-six cases.

2. The same type and intensity of reactions are obtained with this gold sol as with chemically prepared gold.

3. The presence of blood or blood serum in spinal fluid influences the reduction of the gold sol, and the spinal fluid should always be tested for blood by the benzidine test. If blood is found present, a notation to this effect should be made on the report submitted to the clinician so that he may properly interpret the result.

4. Typical luetic curves were obtained in 85 per cent of the cases of syphilis of the central nervous system.

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AUTOPSY REPORT OF TWO CASES OF THYMIC DEATH DURING SURGICAL OPERATIONS*

BY JESSIE W. FISHER, M.D., MIDDLETOWN, CONN.

MY object in reporting these two necropsies is not so much to recall to your mind the striking pathologic picture or to discuss the disputed etiology but to get an expression of opinion upon some method to detect these cases before they become operating room tragedies. Any diagnostic method, however time consuming or expensive, is worth while if one life can be saved.

That this condition is rare is one of the greatest fallacies. J. E. Benjamin is quoted by Friedlander as finding two hundred and twenty-five new cases in one year, of these 8.4 per cent showed indisputable evidence of enlarged thymus.[1]

It is not within the scope of this report to discuss the various hypotheses brought forward to explain status thymicolymphaticus itself or the factor which causes death following trivial traumas.

Direct pressure of the thymus, hormones, anaphylactic conditions, faulty metabolism, insufficient adrenalin, overfunction of thymus, etc., are some of the explanations given.

Very interesting and enlightening results are coming from the experimental laboratories. The work of Marine, Manley, and Baumann[2] includes observations of the effects of removal of the thyroid, gonads, and spleen as well as of the suprarenals, upon the thymus. These observations have been made on animals covering a period of ten years. The removal of the thyroid, parathyroid, thymus, spleen, suprarenals and gonads, either alone or in combination have been carefully studied. Three hundred and seventy-three animals are reported upon and the results are summarized as follows:

"Thyroidectomy hastens, while gonadectomy delays, but does not permanently prevent involution of the thymus.

"Suprarenalectomy alone not only delays involution of the thymus and

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lymphoid tissue but may cause their regeneration. Thyroidectomy prevents this reaction, even, after combined suprarenalectomy and gonadectomy.

"Suprarenalectomy plus gonadectomy is a more powerful stimulus for thymus and lymphoid regeneration than either of these influences alone.

"The combined effect of these two factors results in certain lymphoid and thymus hyperplasia in rabbits, which persists until regeneration of accessory interrenal tissue corrects the physiologic defect. The syndrome thus experimentally produced resembles status lymphaticus and is believed to depend mainly on a partial loss of certain functions of the interrenal and sex glands rather than of the chromaffin tissue.

"The normal and abnormal lymphoid and thymic hyperplasia of infancy and childhood are believed to be manifestations of a functional underdevelopment of the interrenal and sex glands of varying intensity.

"The so-called lymphatic constitution which underlies or accompanies exophthalmic goiter, Addison's disease and acromegaly also appears to be dependent on a partial suppression of certain functions of the interrenal and sex glands."

It is interesting to note that Jaffe's[3] finding of thymus hypertrophy following suprarenalectomy is sustained by this new work of Marine, Manley and Baumann, for they report: "Suprarenalectomy alone, not only delays involution of the thymus and lymphoid tissue but may cause their regeneration," and that "Gonadectomy delays, but does not permanently prevent, involution of the thymus."

No attempt will be made to review the literature which has been thoroughly covered by Marine, Manley, and Baumann[2] to which paper you are referred.

There is no more tragic occurrence from every point of view than the sudden death on the operating table of patients, apparently in the best of health, who are undergoing trivial operations, such as removal of tonsils, etc.

Within three months we have had at our hospital two such deaths both of which showed the classical changes of status thymicolymphaticus postmortem.

The first death occurred in July, 1924, in a Polish boy, J. M., four years of age (one of twins). He was a stocky, pasty looking, rather short necked child without physical stigmata.

Family history was negative except that father had died of pneumonia the previous summer.

Four children of the same family were admitted to the hospital for tonsillectomy. Two older children were operated upon; both took the ether rather poorly, showing cyanosis, but nothing to alarm the etherizer. They also came out of ether poorly but were discharged the following day in good condition.

One subsequently died of what was said to be pneumonia, presumably postoperative, but we could get little information on this subject because of the feeling of the mother in regard to the tragedy. The fourth child was not operated upon on account of the death of the twin.

The preanesthetic examinations revealed nothing to forecast the tragic event. The urine examination was negative.

The child was well under ether (anesthetic, straight ether) and the operation was but just begun, when the patient ceased to breathe. No cyanosis was noted. All the

usual methods including lungmotor, intracardiac hypodermic of adrenalin, etc., were of no avail.

At autopsy the postcervical and elbow lymphatic glands were found palpable. The axillary and inguinal glands were not palpable.

All adipose tissue was a peculiar lemon color.

The thymus gland was firm and lobulated and extended to the fifth interspace. Weight 37.8 grams, left lobe 10 cm. long, right lobe 8 cm. Heart was in systole and the aorta was rather narrow but not specially striking.

No blood, mucus, or other obstruction was found in respiratory tract and lungs were normal.

Tracheobronchial lymph nodes, thoracic duct and lumbar nodes as well as entire lymphatic system showed marked hyperplasia. Glands were firm in consistency and pinkish in color. In other words, they had all the gross appearance of a giant edition of a normal gland.

Fig. 1.—J. M. Thymus gland, weight 37.8 grams.

The mucosae of the small intestine was thickly studded with hyperplastic lymph nodes, varying from pinhead to small shot in size, elevated above the surface like a cauliflower, giving the entire gut a pebbly appearance.

Solitary follicles and Peyer's patches were enormously enlarged. Some of the latter measured 6 to 7 cm. in length.

The large intestine showed similar but not quite such striking changes.

The mesentery was a mass of hyperplastic lymph nodes varying from 1 cm. to 3 cm. in diameter, single and coalescing.

Adrenals showed no gross pathology though they were small and soft.

The spleen weighed 90 grams, and was 10 cm. long by 6.1 cm. wide. On section, the tissue was firm but thickly studded with greyish white masses, the size of a pinhead. (Giant hyperplasia of malpighian bodies.)

Testicles were both descended and normal in size and appearance.

Blood smears taken at autopsy showed small lymphocytes 88 per cent, polymorphonuclears 7 per cent, and large mononuclears 5 per cent.

Wassermann; negative.

Head was not opened.

Microscopic examination showed giant hyperplasia of all lymphoid elements; otherwise, not essentially different from the normal histology.

The second case occurred in October, 1924, three months later.

S. C., aged ten years, Italian, born in America.

The child was rather slightly built, general appearance did not suggest the so-called thymicolymphatic syndrome.

Family history was not of especial significance.

Previous attack of appendicitis a year ago, otherwise personal history without interest.

The boy had been sick for two days before a physician was called. He was ordered to hospital at 10 A.M., but family refused to send him till evening (7:50 P.M.).

On admission he presented a classical picture of ruptured appendix. Tonsils were small, thyroid palpable but no other glandular enlargement noted. Aside from a slight cyanotic hue, there was nothing to suggest thymicolymphaticus.

Blood Count: A.M. 12,200; Polys., 80.5 per cent; S. L., 13.5 per cent; L. L. 5 per cent.

Fig. 2.—J. M. Mesenteric glands.

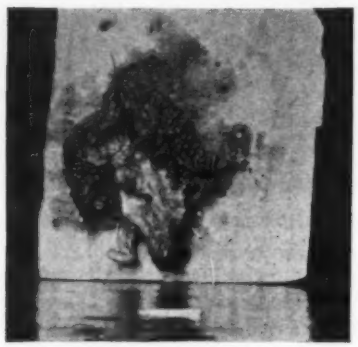

Fig. 3.—J. M. Peyer's patch, 7 cm. in length.

Blood Count: P.M. 13,400; Polys., 68 per cent; S. L., 28 per cent; L. L., 5 per cent.

Neither urine examination nor Wassermann tests were made.

Anesthesia, began at 9:15 P.M., was straight nitrous oxide; after twenty seconds, oxygen and in two minutes, ether was added.

Pupils were widely dilated.

Pulse, 100 to 120.

As soon as appendix was delivered, ether was discontinued except that on two occasions a small amount of ether was added to nitrous oxide-oxygen mixture when respirations became very slow. A few breaths of ether brought respirations up to normal. Thirty-five minutes after the operation was begun, the patient was pronounced dead.

When closing of peritoneum began, patient's condition was good. Gas was decreased and oxygen increased, so the two were of about equal volume.

When sewing of fascia was begun the pupils began to contract, respiration became slow and shallow and suddenly stopped entirely. At no time was there cyanosis or rigidity.

Artificial respiration, breathing tube, epinephrin intracardially, etc., were used but without results.

The appendix was ruptured and imbedded in a mass of inflammatory exudate with localized hemorrhage and peritonitis.

Autopsy, nine hours postmortem. Aside from the evidence of recent appendectomy, the adenopathy was the most striking feature.

Blood changed to bright red on exposure to air.

The thymus gland covered aorta and base of heart. Weight 29.2 grams; left lobe length 9.5 cm.; right lobe 8.3 cm. The gland was firm, lobulated and pinkish in color.

Mesenteric lymph nodes were prominent. They were irregular in size and shape, varying from size of a shot to 2 cm. in diameter, pinkish in color, firm in consistency, and there was no evidence of necrosis.

Stomach wall was thickened; contents consisted of small amount of bloody mucus. Mucosae showed hemorrhagic areas 2 to 4 cm. in diameter. Entire ileum showed hyperplasia of lymphoid tissue.

Peyer's patches measured from 2 to 3 cm. in length, were nodular and some were hemorrhagic. Hyperplasia was not so marked as in previous case.

Adenopathy was most marked in terminal ileum and from cecum to rectum.

Fig. 4.—S. C. Thymus gland, weight 29.2 grams.

Spleen weighed 80 grams; trabeculae were fairly prominent; lymphoid hyperplasia was manifested by minute greyish masses throughout the pulp (not so prominent, however, as in previous case).

Suprarenals were small and soft in consistency.

Liver, gall bladder, and urinary bladder were essentially negative.

The kidneys were congested.

Except for rather narrow vessels, there was nothing unusual about the heart.

Larynx, trachea and esophagus were all free from obstruction, blood or mucus, but the bronchi contained a small amount of bloody mucus.

Right lung weighed 200 grams and presented many small areas of atelectasis and three subpleural hemorrhages, irregular in shape; 3 to 4 cm. in diameter, in lower lobe. These hemorrhagic areas were filled with extravasated blood and frothy mucus.

The lower lobe of the left lung was studded with small subpleural hemorrhages similar to those in the right.

Smears and cultures were negative.

Peribronchial glands were similar to mesenteric glands.

Thoracic duct was hyperplastic as were all the subperitoneal and pelvic glands.

Genitalia normal. Testicles normal in appearance.

Brain (weight, 1300 grams) showed tremendous amount of pial congestion with slight edema.

Cerebral vessels were engorged but there were no hemorrhages or other pathology.

The microscopic picture differs in no essential from the normal thymus and lymph glands except in the hyperplasia of lymphoid tissue.

The gonads were not examined microscopically.

The second case was quite unusual as the operative procedures were about finished when death occurred, while in the tonsil case they had just begun.

Both of these cases come under the classification of status thymico-lymphaticus.

Both were males and of foreign parentage.

They were very similar in their adenopathy but differed in that the second patient showed hemorrhagic areas in lungs, stomach walls and Peyer's patches, which probably were due to the effects of infection.

In both cases, the suprarenal glands were small and soft.

Fig. 5.—S. C. Mesenteric glands.

The gonads showed no gross abnormality, but unfortunately were not examined microscopically.

In the second case, the family threatened to bring suit against the hospital, technically, because of autopsy without their permission (coroner had given a verbal order of which their lawyer apparently had no knowledge) but really in the hope of proving malpractice.

The coroner, therefore, held a public inquest at which he courteously permitted the Italian lawyer, engaged by the family, to question the witnesses.

The entire drift of the lawyer's questions were to the effect that the condition ought to have been recognized prior to operation. "If x-rays would show it, why weren't x-rays taken?"

I think the lawyer's implied criticism was justified, though in this particular case, the operation was not one of election.

To those of us who work in small cities, where any unusual case is broadcast by more or less loving (?) friends of the hospital, these cases resolve themselves into three distinct tragedies.

First and foremost, of course, the individual and family tragedy.

Second, the surgical tragedy, i.e., the effect upon the morale of the surgeon, anesthetists and assistants.

Third, the hospital and community tragedy.

Both of these tragedies have been broadcast throughout the county with much adverse criticism of the hospital and the surgeons. The laity just cannot believe that a child can go onto an operating table in good health, and be dead in a few minutes unless some one has grossly blundered.

In large cities, these cases are individual tragedies, not community affairs as they are with us. They, of course, in every instance, except in emergency operations, could be avoided by careful x-rays, and with treatment, these patients might possibly survive the vicissitudes of childhood and become healthy individuals.

REMARKS

A careful physical examination may fail to give the slightest clue to adenopathy.

A lymphocytosis is, of course, suggestive but not pathognomonic especially when cases are complicated by infections as in our second case.

A carefully interpreted preoperative x-ray seems to be the most reliable method of eliminating these casualties though even this fails us when the thymus is not involved.

The Middlesex Hospital has attempted to guard against future accidents by making a rule that all children up to fourteen years of age must have a thymic x-ray before elective operative procedures are undertaken.

If there are any other diagnostic suggestions we will be only too glad to hear them.

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ACTION OF BENZYLAMINE UPON CIRCULATION, SMOOTH MUSCLE, AND RESPIRATION*

By George R. Love, M.D., and J. B. Waddell, M.D., Chicago, Ill.

BARGER and Dale[1] mention benzylamine as having a mere trace of sympathomimetic or adrenalin-like action. Since their experiments were quite limited, a more intensive study of benzylamine seemed justified.

Benzylamine was dissolved in distilled water, neutralized with HCl until

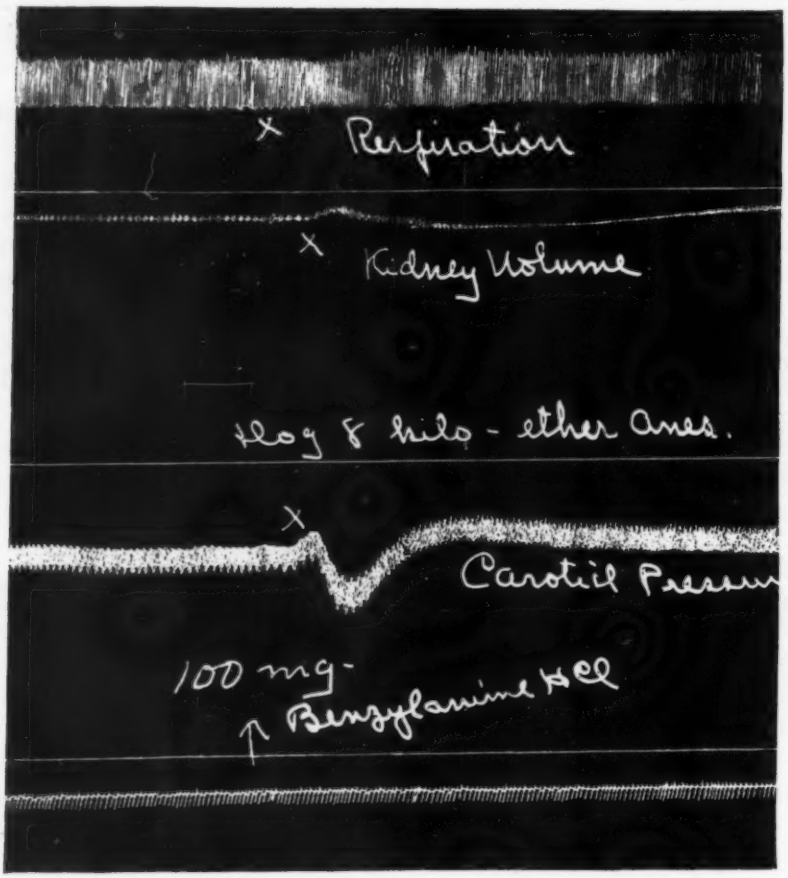

Fig. 1.—A typical effect upon blood pressure, kidney volume, and respiration after the first dose of benzylamine.

barely alkaline (litmus), and diluted with distilled water to make a 5.0 per cent or 10.0 per cent solution in terms of benzylamine.

All in situ experiments were performed upon dogs under light ether anesthesia by tracheotomy.

*From the Department of Pharmacology and Therapeutics of the University of Illinois, College of Medicine.
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BLOOD PRESSURE

The intravenous injection of 100 to 200 mg. of benzylamine produces a primary fall of blood pressure which is usually followed by a variable rise above the original level (see Figs. 1, 2, 3). The rise of pressure, when it occurs, lasts only a few moments, at which time the dose may be repeated with practically the same effect. After several injections, the blood pressure assumes a lower level which persists until the end of the experiment, which

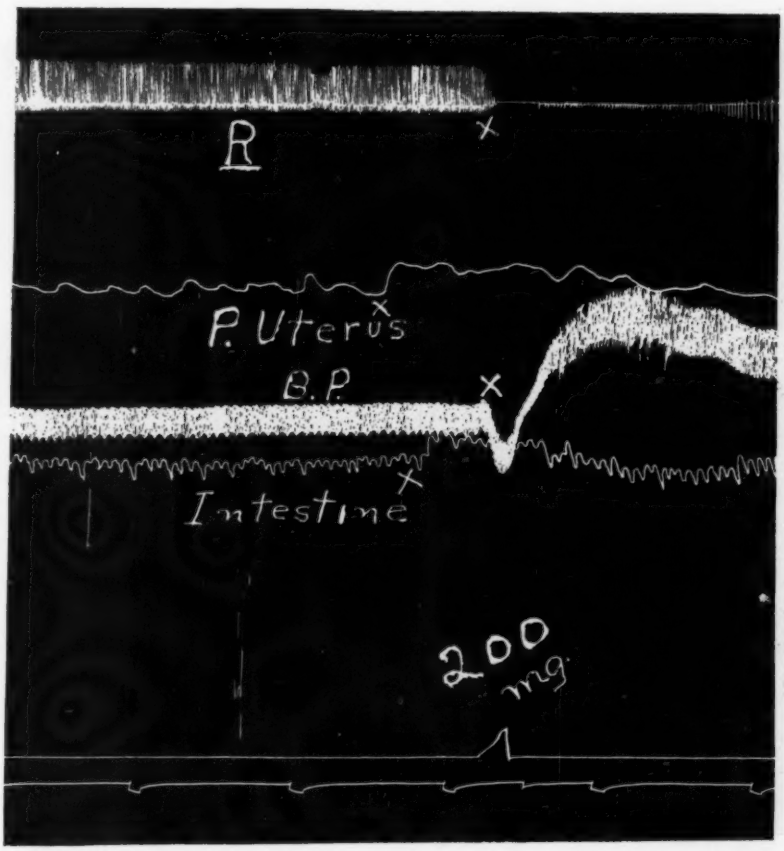

Fig. 2-*A*.—Dog, 10 kilograms, surgical anesthesia (ether). Note a very slight stimulation of both uterus and intestines. This stimulation is not, however, constant. The rise of blood pressure in this dog after benzylamine is higher than usual.

in this work usually lasted for two or three hours. Larger doses, administered rapidly, cause an abrupt fall of pressure, cardiac dilatation, and cessation.

Occasionally after a large dose, the blood pressure falls, begins to rise, and then suddenly falls to zero. On inspection the sudden fatal fall of pressure appears to be due to acute dilatation of the heart, which is usually followed by ventricular fibrillation (see Fig. 4).

THE HEART

The primary fall of blood pressure is due chiefly to cardiac depression. The proof is as follows:

1. The heart dilates (cardiometer) and usually the rate decreases on the fall of pressure.

2. The plethysmograph tracings of abdominal viscera and extremities follow the blood pressure curve downward.

3. The action occurs after section of vagi and administration of atropine.

4. Large doses, as 30 to 50 mg. per kilogram, cause acute dilatation and usually cessation of the heart action.

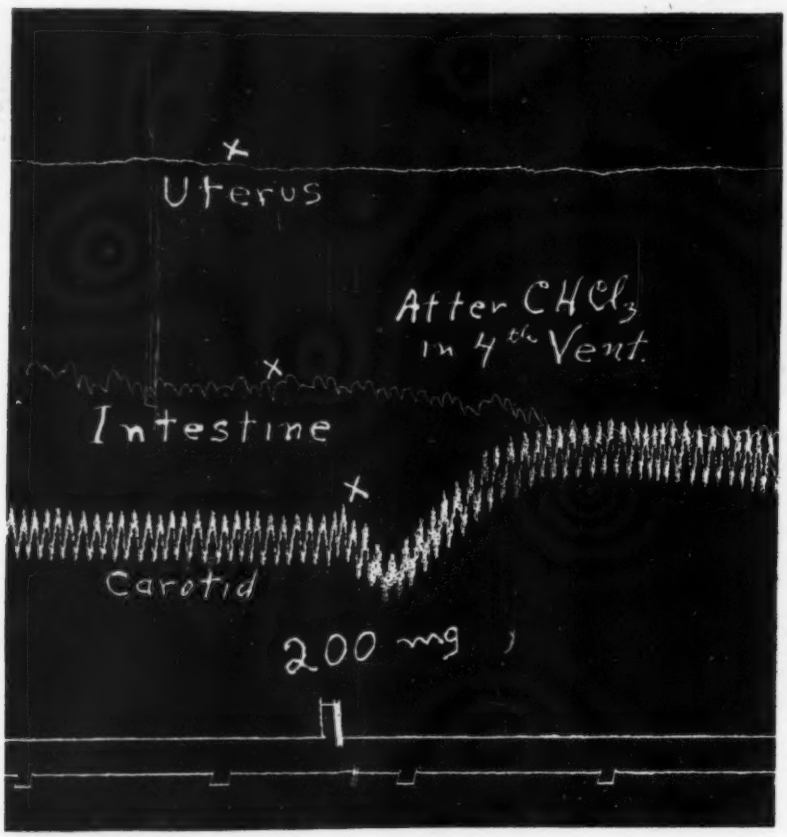

Fig. 2-*B*.—Note that the rise of blood pressure occurs after chloroform injections into fourth ventricle. Uterus and intestines are not influenced by this injection.

BLOOD VESSELS

The plethysmograph tracings of the kidney, spleen, intestines, and extremities follow the blood pressure downward, due chiefly to the cardiac depression. When, however, the blood pressure recovers and rises above the original level, the volume levels sometimes remain below the original level, indicating peripheral constriction. The mechanism of the after-rise of blood pressure is attributed to peripheral constriction and cardiac recovery (see Figs. 1 and 3). This peripheral constriction or rise of pressure occurs after chloroform injections into the fourth ventricle (technic 2) and is therefore not of central origin (see Figs. 2-*A* and 2-*B*).

On perfusion with Locke's solution, 37° C., 120 mm. Hg., the extremities show a definite decrease of outflow after benzylamine. The results from perfusing the kidneys are variable, but more often show a constriction. Several perfusions were made upon extremities before and after ergot and atropine (using epinephrin as an indicator for neuromuscular constrictor paralysis). The benzylamine constriction occurs equally well after ergot and atropine. Excised aortic rings also are stimulated by benzylamine after ergot and atropine (see Fig. 5).

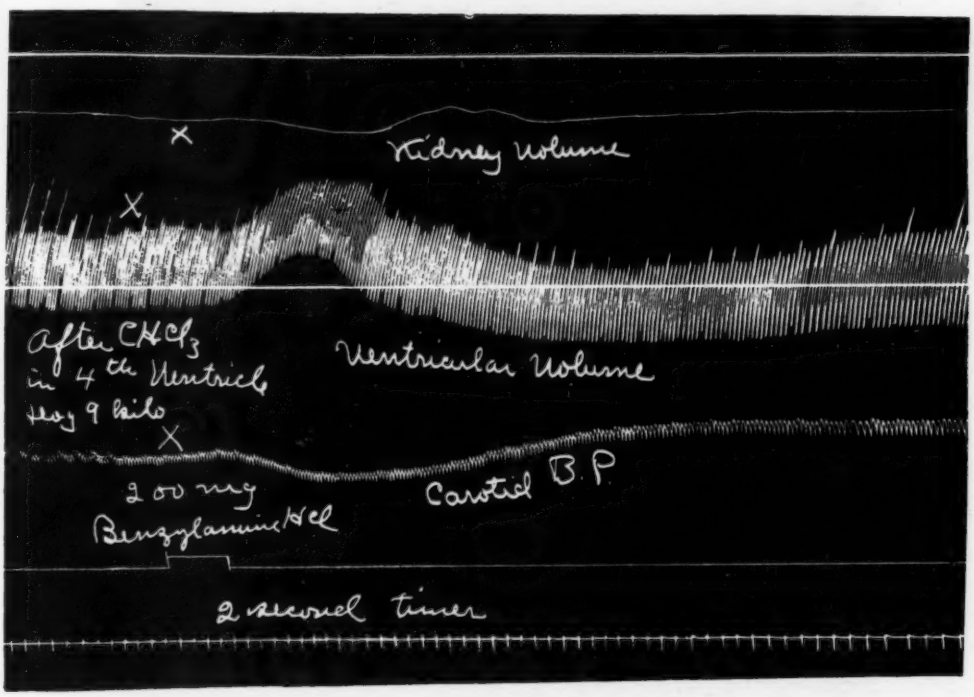

Fig. 3.—Note the acute dilatation of the heart and rapid recovery.

PULMONARY CIRCULATION

The pulmonary pressure usually rises from 5 to 30 mm. H_2O following 5 to 10 mg. per kilogram doses of benzylamine, while the carotid pressure falls. This rise may be attributed in part to back pressure, since the left ventricle is more sensitive to cardiac depressants than the right ventricle, and in part to pulmonary constriction. Larger doses produce a simultaneous fall of both carotid and pulmonary pressures, which is of cardiac origin. These effects are illustrated in Figs. 6-*A* and 6-*B*.

On perfusing the lungs under a constant pressure, the introduction of benzylamine causes a definite decrease of the outflow. The excised pulmonary arteries are likewise stimulated by benzylamine. (Technic 4; see Fig. 5.)

The circulatory action of benzylamine may be summarized as cardiac depression and mild constriction of the arteries, both actions occurring directly upon the muscle independent of nerve supply.

STOMACH

The amplitude of the movements and tone of the intact dog stomach is increased by 5 to 20 mg. per kilogram doses of benzylamine (technic 3). The action occurs, though less marked, after atropine (see Fig. 7). After repeated doses of benzylamine the stomach fails to respond.

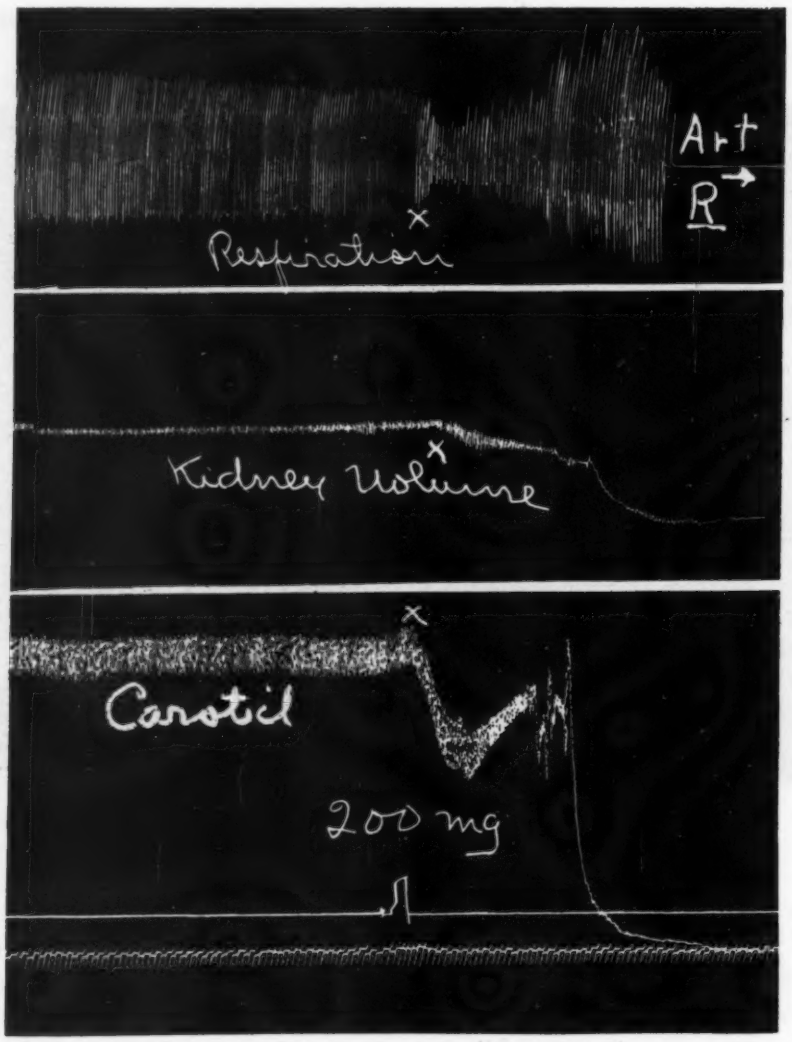

Fig. 4.—Dog, 8 kilograms. The cause of death was ventricular fibrillation. The kidney volume remains low on the recovery of pressure preceding fibrillation.

INTESTINES

Benzylamine has no definite constant action upon the intact dog intestines (see Figs. 2 and 7).

BLADDER

The intact dog bladder is very sensitive to benzylamine. Small doses, 3 to 10 mg. per kilogram, which sometimes do not materially affect the stomach

and circulation, definitely stimulate the dog bladder (technic 3). Larger injections, up to circulatory failure, cause a proportionately greater contraction. This action occurs equally well after atropine.

UTERINE HORNS

The intact uterine horns of dogs, both pregnant and nonpregnant, are occasionally slightly stimulated by benzylamine injections. The action is not, however, definite or constant as upon the bladder or stomach (see Fig. 2).

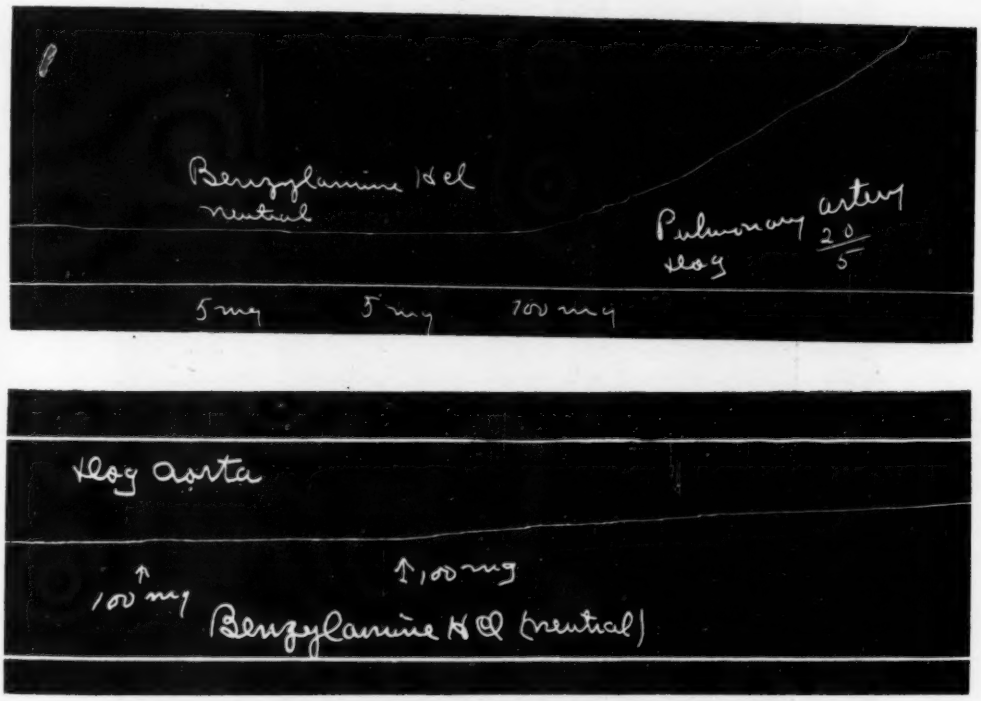

Fig. 5.—The excised pulmonary artery and aorta are stimulated by benzylamine.

EXCISED TISSUES

Excised smooth muscle tissues from the cat, rabbit, and guinea pig were examined by the usual technic, that is, 30 c.c. container, Locke's solution, 37° C., and a constant stream of oxygen or air.

The Cat.—The stomach, intestines (large and small), urethra, uterus (all nonpregnant), and bladder were stimulated by 5 to 25 mg. doses. Of these tissues the bladder is by far more sensitive and vigorous in response to benzylamine. Larger doses, as 100 to 300 mg., usually produce a toxic action in which, although the tissue sometimes does not relax completely, it will not respond to barium chloride. The stimulating action of the smaller doses occurs after administering atropine and ergot.

The Rabbit.—The pregnant and nonpregnant uterus, as well as the other tissues mentioned above, were examined with practically the same results.

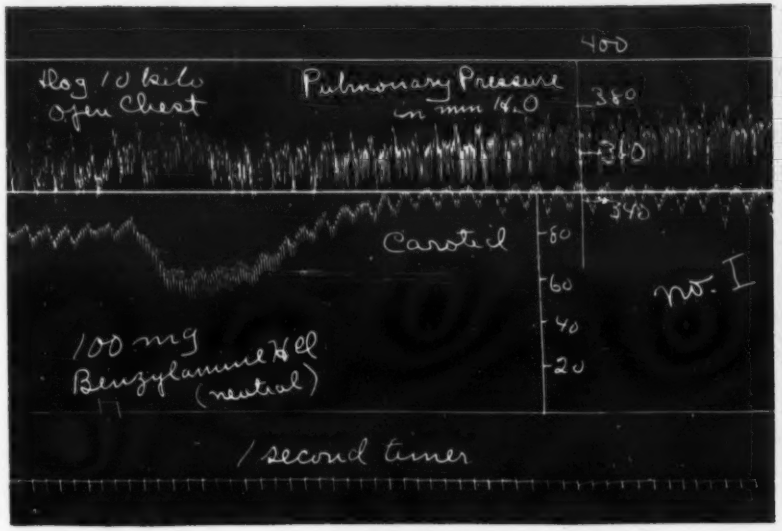

Fig. 6-*A*.

Fig. 6-*A*.—Ten mg. per kilogram cause a slight rise of pulmonary pressure and a fall of carotid. Note that pulmonary pressure rises again with the carotid.

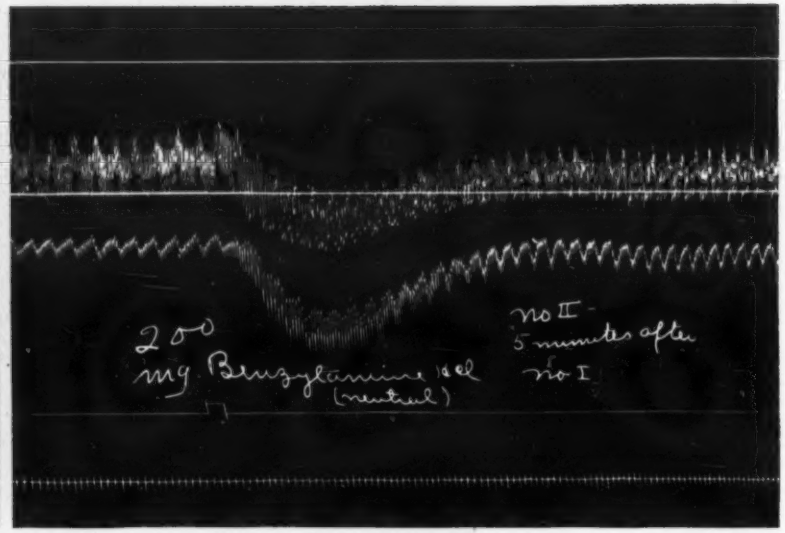

Fig. 6-*B*.

Fig. 6-*B*.—A larger dose produces a fall of both pulmonary and carotid pressures, due to profound cardiac depression.

The rabbit stomach and intestines were, however, less resistant to depression from increasing doses than the corresponding cat tissues.

The Guinea Pig.—The stomach, intestines, uterus (pregnant and non-pregnant) are usually depressed by an effective dose of benzylamine. Occasionally these tissues may show a very mild pressor action after a small dose of from 2 to 5 mg. The effective doses of 10 to 50 mg. produce a definite relaxation from which the preparation recovers in a few moments. Larger doses produce permanent depression and loss of barium chloride response.

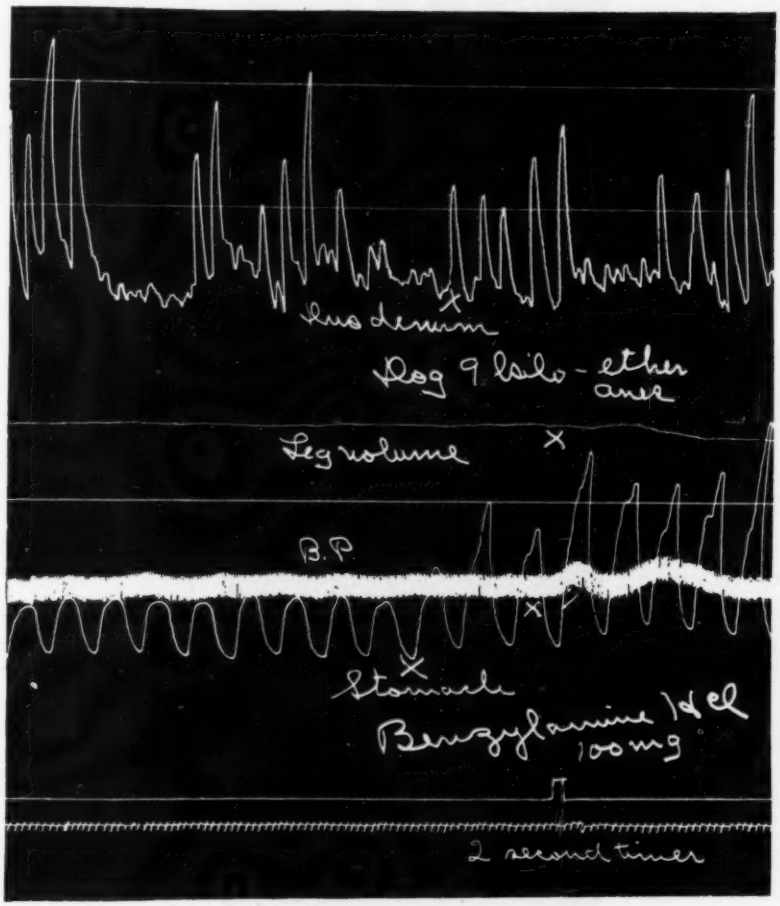

Fig. 7.—The stomach is distinctly stimulated by the first dose of benzylamine. Subsequent injections do not produce such a definite action.

The guinea pig bladder is distinctly stimulated by benzylamine, and is much more resistant to depression from larger doses than the other pig tissues examined. The stimulating action occurs after the administration of atropine and ergot (see Fig. 8).

RESPIRATION

The respiration of dogs under very light ether narcosis is stimulated by the first effective dose, usually 5 to 10 mg. per kilogram. The stimulation is evanescent and may be due in part to the circulatory changes. Repeated

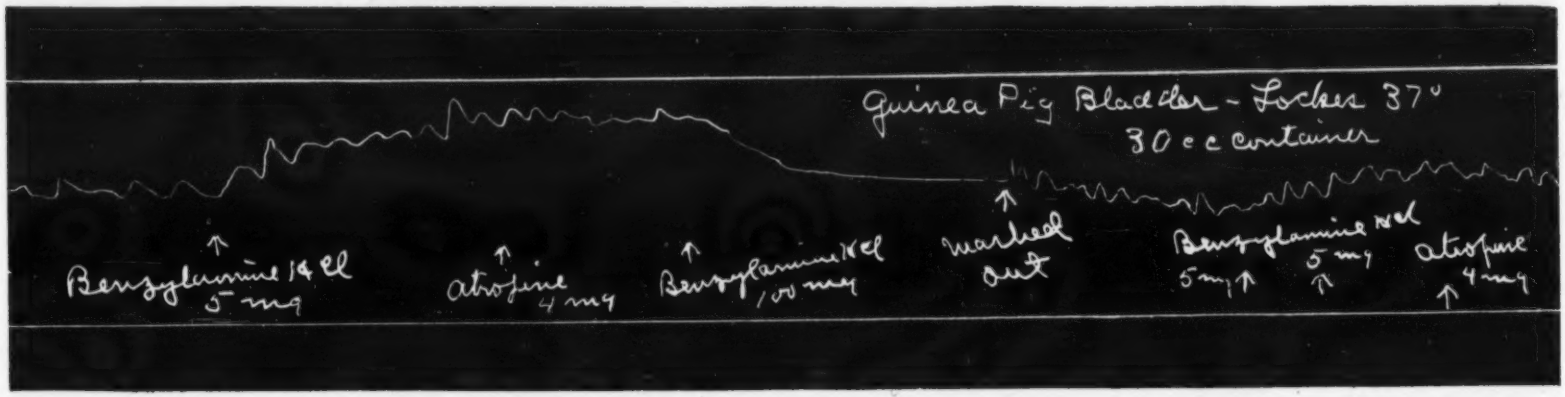

Fig. 8.—Excised guinea pig bladder is distinctly stimulated by benzylamine in small doses after atropine and ergot (ergot not applied on this particular preparation). Large doses cause a depression from which the tissue can recover by washing out.

injections cause a depression and finally a cessation of respiration. Under surgical anesthesia an effective dose usually causes depression. Respiratory failure is the cause of death from increasing doses; however, a large rapid injection of 30 to 50 mg. per kilogram causes a simultaneous failure of both the heart and respiration. The respiration of unanesthetized dogs is not influenced by benzylamine until other actions cause the animals to struggle.

CONCLUSIONS

1. Benzylamine is a cardiac depressant, acting directly upon the heart muscle.

2. The perfused, and excised vessels, including the pulmonary arteries, and usually the intact systemic arteries, are constricted by benzylamine. The action is presumably direct upon the muscle, since it occurs after doses of atropine and ergot.

3. Other excised smooth muscle, such as the stomach, intestines, uterus, and bladder, are stimulated by small doses and depressed by larger doses. The relative action varies in different animals and different tissues of the same animal. The bladder of all animals examined responds more vigorously to benzylamine than other smooth muscle examined.

4. The intact stomach and bladder of dogs are stimulated by benzylamine; they are not depressed by doses which cause circulatory failure. The intact intestine and uterus of the dog are not decidedly influenced by any nonlethal dose.

5. The respiration of dogs under light ether anesthesia is slightly stimulated by small doses and depressed by large doses.

6. Failure of respiration is the cause of death from graduated doses. A large dose injected rapidly may cause death by simultaneous failure of the heart and respiration.

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A CASE OF SQUAMOUS-CELL EPITHELIOMA OF THE STOMACH*

By Porter P. Vinson, M.D., Section on Medicine, and
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ALTHOUGH squamous-cell epithelioma is a common malignant neoplasm in such locations as the skin, lip, tongue, cervix, and bladder, it is rarely found in the stomach in man. It is, however, often found in the stomach in certain of the lower animals, especially the rat. When one considers the frequency with which carcinoma originates in the stomach, it is rather inexplicable that there are not more of the squamous-cell variety among them. Even the gall bladder which, like the stomach, is lined with columnar or

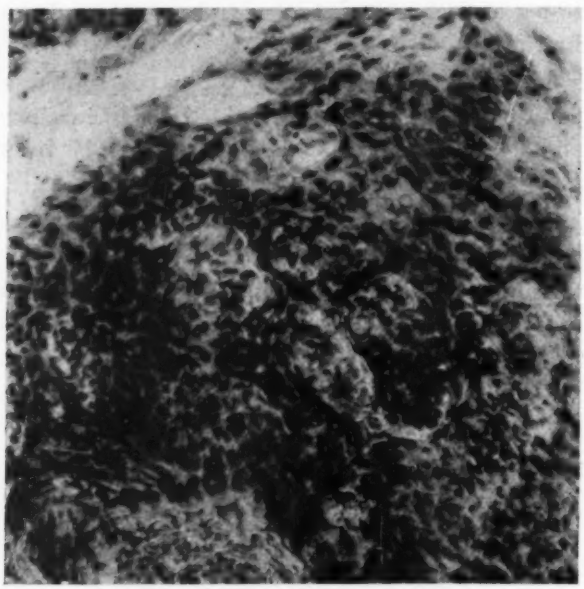

Fig. 1.—Section of stomach showing gland and squamous epithelium, with malignant change in the latter.

secreting epithelium, is the seat of more squamous-cell epitheliomas, although the occurrence of cancer in the gall bladder is comparatively rare.

The question naturally arises of how a squamous-cell epithelioma can originate in an organ lined with columnar or secreting epithelium. The same answer will apply to both stomach and gall bladder; the regenerative cells which normally produce gland or secreting epithelium also produce protective epithelium if necessary, which is shown by the fact that if the uterus becomes inverted and remains so the epithelium of the endometrium changes

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from a gland or secreting type to a squamous or protective type. The following case is an example:

A woman, aged forty-six, was examined in the Clinic, December 30, 1924. She had had an attack of pneumonia at the age of twenty-nine, and following this, obstruction in the lower part of the esophagus to the passage of solid food, unless it was chewed thoroughly. No trouble was experienced in swallowing soft or liquid foods. The dysphagia was thought to be due to a small goiter, but a partial thyroidectomy in 1920 did not afford relief. The trouble continued with about the same degree of severity until January,

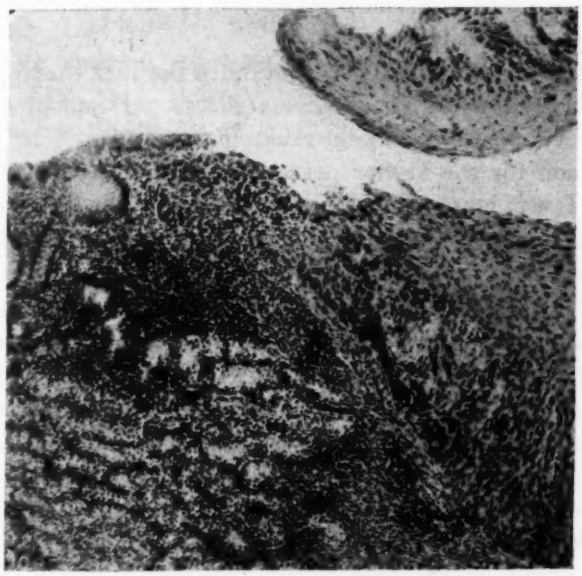

Fig. 2.—High power magnification of typical area of epithelioma.

1924, when obstruction suddenly became complete. Gastrostomy was performed the following day. The patient had lost thirty-eight pounds and had become quite weak.

Examination revealed considerable emaciation and pallor and a firm nodular epigastric mass. December 31, 1924, a small bronchoscope was introduced into the stomach through the gastrostomy opening and a piece of tissue removed from an ulcerating lesion involving the upper half of the organ. Microscopic examination of a section of the growth showed it to be a squamous-cell epithelioma grade 3 (Figs. 1 and 2).

THE SCHICK TEST AND SCARLET FEVER*

By Thomas G. Hull, Ph.D., Springfield, Ill.

FOR some years past, observations have been made in these laboratories upon the relation of the Schick test to a previous history of scarlet fever. Material for these studies has not been extensive, since accurate histories were not obtainable in most instances.

Park and Zingher[1] have called attention to the fact that while 21 per cent of normal children show positive Schick tests, 45 per cent of children ill with scarlet fever give positive Schick reactions. Zingher,[2] in an attempt to explain the reason for the higher percentage of Schick reactions in children ill with scarlet fever, measles, and poliomyelitis, presents two possible causes.

"1. A destruction of the natural diphtheria antitoxin content during an attack of poliomyelitis or of scarlet fever.

"2. A susceptibility to one of the less contagious diseases indicates that the child is also more apt to be susceptible to other contagious and infectious diseases."

From observations made in these laboratories it would seem that an attack of scarlet fever tended to destroy the diphtheria antitoxin present in the circulation, causing the Schick test to become positive.

Scarlet fever histories have been obtained from 130 persons,—30 adults from the State Department of Public Health, 75 nurses from St. John's Hospital, Springfield, 14 children tested by C. A. Earle, of Des Plaines, and 11 children from Mooseheart, Ill. In Table I, it will be noted that of 107 persons showing no previous history of scarlet fever the Schick reaction was positive in 52 per cent while in 23 persons who had had scarlet fever it was positive in 87 per cent. Three persons who had had scarlet fever gave negative Schick tests. Upon inquiry it was found that several years had elapsed since the date of the disease—twenty years, fifteen years and five years, respectively. There is a possibility that the antitoxic immunity to diphtheria, if destroyed by the case of scarlet fever, had been regained through the intervening years.

The possibility of a greater incidence of scarlet fever among persons showing a positive Schick test was considered. Histories on 24 Schick-tested children were found, who later developed scarlet fever. Of this number 16 were Schick-negative previous to the attack of scarlet fever while 8 were Schick-positive. It was unfortunately impossible to get results of Schick tests after recovery from scarlet fever in this group. It is apparent, however, that the presence of diphtheria antitoxin in the blood has no effect upon the incidence of scarlet fever.

*From the Division of Laboratories, Illinois Department of Public Health, Springfield, Illinois.

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TABLE I

RELATION OF SCARLET FEVER TO THE SCHICK REACTION

	TOTAL	SCHICK-POSITIVE	SCHICK-NEGATIVE
Previous history of scarlet fever	23	20	3
No history of scarlet fever	107	56	51

While the cases here cited are so few in number that no definite conclusions can be drawn, it would appear that scarlet fever renders the Schick reaction positive. It is hoped that this report will stimulate similar observations by other workers.

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HYDROGEN-ION CONCENTRATION AS A FACTOR IN THE WASSERMANN AND KAHN TESTS*

BY JAMES HARVEY JENNETT, A.B., A.M., KANSAS CITY, MO.

THERE have been many theories and speculations in recent years regarding the part hydrogen-ion concentration plays in bacteriologic and serologic reactions. Since H-ion studies have become so popular, an explanation of many of the heretofore unexplained phenomena is looked for in them. Various workers[1] have suggested that hydrogen-ion concentration may play an important part in complement fixation and some have urged the use of buffered saline solutions in such tests.

When two oppositely charged colloids, as arsenic trisulphide and aluminum hydroxide, are brought together, a precipitate is formed. Can it be that the precipitate in the Kahn test is due to a similar reaction?

When a slight amount of acid is added in the Kahn routine test a false positive is produced.[2] When a slight amount of alkali is added in the Kahn routine test a false negative is produced. Can the difference between positive and negative results in the routine Kahn be due to acidity factors? When a serum globulin solution is brought to the isoelectric point for globulin it will be precipitated. Is the precipitate in the Kahn test the result of bringing the mixture to the isoelectric point of the colloids? These and other similar questions have caused me to wonder if the real difference between a positive and negative serum, in addition to the difference in globulin content,[3] could be a hydrogen-ion variation.

The following experiments were performed to determine the P_H at which these serologic tests are carried out and to find whether there is any differ-

*From the Department of Bacteriology and Preventive Medicine, University of Missouri, Columbia, Mo.
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ence between the positive and negative or whether a variation in H-ion concentration will cause an alteration in the results.

The Wassermann technic was that used routinely in this laboratory, a sheep cell-rabbit amboceptor system. The Kahn test was carried out in detail as described in Kahn's papers.[4] The sera used were from specimens of blood sent in to the Public Health Laboratory for Wassermann tests, and when larger amounts of individual sera were needed, they were taken from patients in town, and from medical students.

In determining the H-ion concentration, both the colorimetric drop ratio method (Gillespie) and the electropotentiometer method were used. Determinations by the colorimetric method were made on specimens dialyzed through collodion sacs against normal saline (0.85 per cent). Determinations by the electropotentiometer method were made on undialyzed specimens and represent the actual P_H of the solutions.

TABLE I

GILLESPIE'S DROP RATIO METHOD FOR DETERMINING THE RELATIVE PH
(BROMCRESOL PURPLE AND PHENOL RED USED AS INDICATORS)

NO.	MATERIAL	PERIOD OF DIALYSIS	PH
1	Positive serum 4+	15 minutes	6.7
2	Negative serum −	"	6.9
3	Wassermann mixture 4+	"	6.5
4	Wassermann mixture −	"	6.5
5	Complement	"	6.3
6	Antigen	"	5.7
7	Positive serum 4+	24 hours	8.0
8	Negative serum −	"	8.0
9	Wassermann mixture 4+	"	7.3
10	Wassermann mixture −	"	7.2
11	Complement	"	7.0
12	Antigen	"	6.9
13	Positive serum 4+	"	7.5
14	Negative serum −	"	7.5
15	Wassermann mixture 4+	"	7.1
16	Wassermann mixture −	"	7.1
17	Complement	"	6.8
18	Antigen	"	6.7
19	Antigen not dialysed		5.3
20	Saline (0.85%)		6.1

DISCUSSION

The variations in the accompanying tables are to be expected because of the age of the sera when tested. They were from twelve to seventy-two hours old depending on the time it took for them to be delivered to the laboratory. These are representative sera, however, and the conditions were kept the same as when the daily tests are run. These results are a fair representation of the actual P_H of the mixtures in these routine serologic tests. The results show that there is no difference in P_H between positive and negative sera when examined alone, in Kahn mixtures, and in Wassermann mixtures. The H-ion concentration does not seem to play a very important part in these reactions as long as it is kept in a normal range. Complement fixation and precipitation both take place within considerable range of P_H, the optimum

TABLE II

ELECTRICAL HYDROGEN-ION MACHINE METHOD FOR DETERMINING THE ABSOLUTE P_H.

(The machine used was that in the Physical Chemistry laboratory of the University of Missouri. The electrodes used were of platinum and of calomel. The P_H is calculated from the formula:

$$P_H = \frac{\text{Volts}—0.245}{0.0591}.)$$

NO.	MATERIAL	WASSERMANN RESULTS		VOLTS ON POTENTIOMETER	ACTUAL PH
		Cholesterol Antigen	Alcohol Antigen		
1	4+ Serum (heated)	4+	2+	0.730	8.20
2	4+ " (unheated)	4+	–	0.713	7.92
3	4+ " "	4+	–	0.719	8.02
4	4+ " (heated)	4+	4+	0.730	8.20
5	– " "	–	–	0.730	8.20
6	4+ " "	4+	4+	0.745	8.46
7	– " (unheated)	–	–	0.745	8.46
8	– " (heated)	–	–	0.742	8.10
9	4+ Wassermann mixture	4+	4+	0.730	8.20
10	– Wassermann mixture	–	–	0.690	7.53
11	Complement (1–10)			0.668	7.15
12	Antigen (1–10)			0.520	4.65
13	Saline (0.85%)			0.537	4.94
14	Completed Wassermann + R B. C. + amboceptor	4+		0.719	8.04
15	Completed Wassermann without R. B. C.	4+		0.727	8.15
16	Completed Wassermann + R B. C. + amboceptor	–		0.701	7.72
17	Completed Wassermann without R. B. C.	–		0.735	8.28
18	Complement 48 hours old			0.681	7.37
1	Fresh positive serum	2+	–	0.714	7.93
2	" " "	4+	4+	0.725	8.12
3	" " "	4+	4+	0.723	8.08
4	" " "	4+	1+	0.737	8.32
5	" " "	4+	1+	0.715	7.95
6	Saline (0.85%)			0.489	4.09
7	4+ Kahn mixtures	4+	4+	0.724	8.12
8	4+ Kahn mixture	4+	4+	0.718	8.00
9	– Kahn mixtures	–	–	0.735	8.29
10	– Kahn mixture	–	–	0.719	8.04

being at about P_H 8. Nearly all serum reactions done in laboratories are done at a P_H of around 8.

Complement fixation occurs from P_H 5 to P_H 9[5] and between these points the hydrogen-ion concentration does not explain or influence the results.

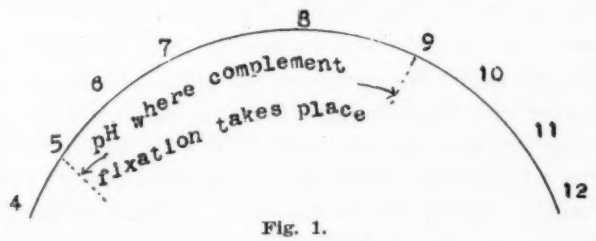

Fig. 1.

The degree of complement fixation rises with the P_H to a certain optimum and then falls again as the P_H becomes too high, the apex of the curve being at P_H 8 (Fig. 1). When false positives are produced in a negative serum by the addition of acid, the buffer effect of the small amount of serum used was over-

come and the solution taken out of the range for complement fixation or precipitate formation. The reaction is now due to excess acid. Blood serum is too highly buffered to undergo any significant change or variation in these tests as far as the hydrogen-ion concentration is concerned.

CONCLUSION

Positive and negative sera, alone and in all the Wassermann and Kahn combinations, show no significant difference one from the other in hydrogen-ion concentration. As long as the P_H is within a certain range it is not a factor in the Wassermann and Kahn tests.

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[1]Mason and Sanford: Jour. Lab. and Clin. Med., February, 1924, ix, 313.
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[4]Kahn, R. L.: Arch. Dermat. and Syph., May, 1922, v, 570.
[5]Morgan: Jour. Immunol., November, 1923, viii, 449.

THE USE OF LIVING VEGETABLE TISSUE FOR SECURING A FAVORABLE GASEOUS ENVIRONMENT FOR ANAEROBIC BACTERIA*

By W. R. Carroll, M.S., Urbana, Ill., and E. G. Hastings, M.S., Madison, Wis.

THE constant stream of papers, presenting methods for the isolation and continued cultivation of anaerobic bacteria, indicates the absence of a satisfactory method. We hope pardon may be granted by the readers hereof if the points suggested do nothing to simplify the present technic.

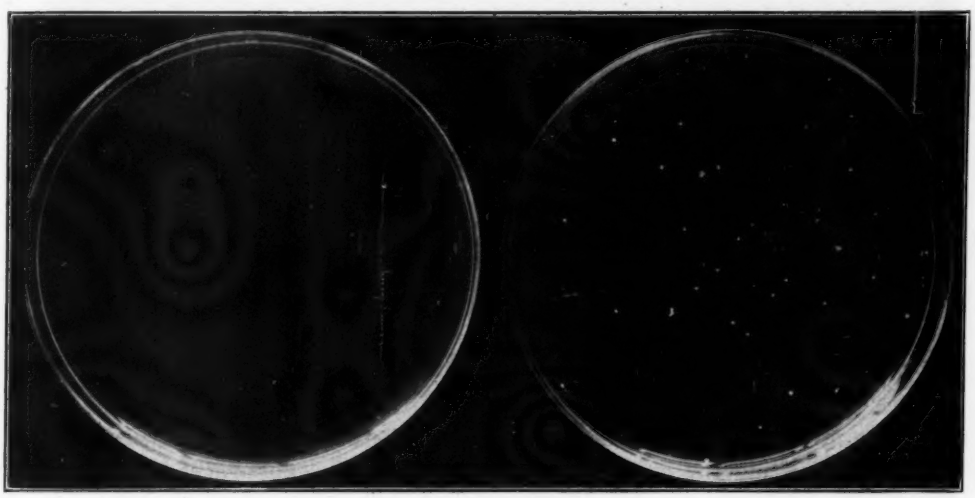
Two conditions with reference to the gaseous environment of anaerobes seem essential for their best development. First: that no free oxygen shall be present, a condition difficult to obtain with methods of replacement or evacuation. Second: the presence of a small percentage of CO_2. The method of Rockwell[1] who has proved the value of this gas in favoring the growth of anaerobic bacteria, is the only one in which such a condition is obtained.

It occurred to us that living plant tissue in the container, in which plates or tubes seeded with anaerobic organisms are to be incubated, should provide an absence of free oxygen and an amount of CO_2, equal to the oxygen absorbed, since the respiratory coefficient is approximately one. The use of such an agent would thus imply no change in volume of the gas in the containers other than that caused by temperature variations. This would be so slight as not to demand complicated means of closing any vessel contain-

*From the Laboratories of the Department of Agricultural Bacteriology, University of Wisconsin.
Received for publication, May 13, 1925.
[1]Rockwell, George C.: Jour. Infect. Dis., 1924, xxxv, 581-586.

ing the cultures. Trials with the method have yielded most satisfactory results. Plate culture No. 1 in Fig. 1 was seeded with *B. granulobacter pectinovorum,* an organism very sensitive to free oxygen, and incubated under aerobic conditions. Plate culture No. 2 in Fig. 1 is a similar plate incubated in an atmosphere from which the oxygen had been removed by potato and to which CO_2 had been returned by the same agent. Plate No. 1 in Fig. 2 is a giant colony of *B. granulobacter* which developed in an atmosphere free of both oxygen and CO_2. The usual alkali and pyrogallic acid mixture was used. Plate No. 2 in Fig. 2 was incubated in an atmosphere free of oxygen, but containing CO_2. Potato was the active agent.

The following organisms have given good surface growth under these conditions; various strains of *B. granulobacter pectinovorum, Clostridium botulinum, Clostridium chauvei* and *Clostridium oedematismaligni.*



1. *2.*

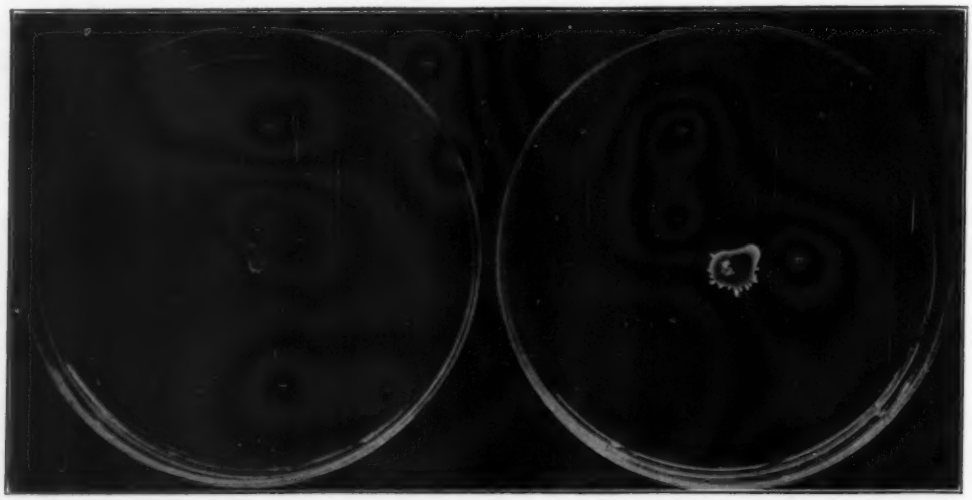
Fig. 1.—Showing dilution cultures of B. granulobacter pectinovorum. *1,* Petri dish No. 1, incubated under aerobic conditions. *2,* Petri dish No. 2, incubated under bell jar with chopped potato.

Tube cultures may be placed in a large test tube in the bottom of which has been placed cubes cut from a well washed and peeled raw potato. A large amount of fresh surface is thus exposed and oxygen is rapidly absorbed. On more completely macerated tissue bacteria present are likely to grow before the end of the incubation period. The large tube may be sealed with a rubber stopper. Since there is no especial change in volume of gas, other than that produced by the cultures or through the growth of bacteria on the potato, the stopper will neither be drawn in nor blown out. An ordinary desiccator or a museum jar with a flat glass cover sealed with plasticine may be used. Tubes or plate cultures may be placed under a bell jar set in a basin or other vessel and a seal of mercury or heavy oil used. In this case the potato is placed in an inner container.

We have little information concerning the amount of potato needed per liter of enclosed air. It is probable that a small amount of tissue will use

up all the free oxygen if time is not to be considered. We have used about fifty grams of potato per liter of air. Germinating oats and lettuce have been used, however, potato seems to be the cheapest and most available material.

Sterile milk to which sufficient sterile methylene blue solution has been added to give a distinct color is an excellent indicator for anaerobiosis. When free oxygen is absent, the milk will reduce the methylene blue.



1. *2.*

Fig. 2.—Showing giant colonies of B. granulobacter pectinovorum. *1*, Petri dish No. 1, under bell jar with alkaline pyrogallic acid. *2*, Petri dish No. 2, under bell jar with chopped potato.

The method suggested has, we believe, the following advantages: It is simple, permitting the culture of anaerobes with the apparatus ordinarily on hand in any laboratory; it is inexpensive, the absorbing medium being cheap and available at all times; and it is effective, since it gives the most favorable gaseous environment for anaerobic cultures.

ANTIGENIC VALUE OF VARIOUS TISSUE EXTRACTS IN KAHN TEST*

By Pearl L. Kendrick, B.S., Lansing, Mich., and H. G. Dunham, B.S., Detroit, Mich.

AN attempt was made to determine the relative potency of various tissue extracts when used as antigen in the Kahn precipitation test. The problem was of interest from the standpoint of the relative distribution of antigenic substance in various organs. It was also of practical importance since such a comparative study would indicate whether heart muscle, so widely used in antigen preparation, contains more antigenic substance than other tissues—particularly those rich in cellular material, such as liver.

By preparing extracts from various powdered tissues according to a uniform method, such as is used for the preparation of Kahn antigen, and testing these antigens with serums in the Kahn test, it seemed that a relatively true comparison of the amounts of antigenic substance in the different tissues could be obtained.

EXPERIMENTAL

Seven beef tissues; namely, heart, liver, kidney, tonsil, lung, spleen, and brain were employed in the experiments. They were prepared as follows:

Preparation of Powdered Tissue.—The different tissues were removed from the beef as soon as possible after the animal was killed. The tissues were immediately put into ice water and taken to the laboratory for preparation. Each tissue was carefully trimmed with a knife to remove as much fat as possible. Foreign tissue and blood vessels were also carefully removed. The trimmed tissue was sliced in thin layers and washed thoroughly with cold tap water to remove the blood as completely as possible. The washed tissue was drained, minced to a paste, spread in thin layers and dried *in vacuo*. The dried material was then powdered by grinding in a ball mill.

Preparation of Antigen.—An extract was prepared from each powdered tissue according to the standard method for preparing Kahn antigen.[1] (The filtration time during the periods of extraction with ether could not be kept absolutely the same in all cases as some of the tissue (ether mixtures) filtered more slowly than others. The brain tissue gave the greatest difficulty in filtration and in this case it was necessary to resort to a Buchner filter.) Each antigen was titrated according to the Kahn method to determine the amount of salt solution required in its dilution for the tests.

Tests with Serum.—The seven antigens were diluted according to titration and tested for their relative sensitiveness in the Kahn test with 120 serums of varying potency. The results are shown in Table I. These findings indicate

*From the Bureau of Laboratories, Michigan Department of Health, Lansing, Michigan, and from the Bacteriological Laboratories, Digestive Ferments Co., Detroit, Mich.
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that the antigenic extract of heart tissue is the most sensitive of the antigens tested. Next in sensitiveness is extract of liver. Extracts of kidney, tonsil, lung, spleen and brain follow in order,—brain tissue producing the least sensitive extract of all.

TABLE I

COMPARATIVE SENSITIVENESS OF ANTIGEN EXTRACTS OF VARIOUS TISSUES

NUMBER OF SERUMS	EXTRACTS PREPARED FROM BEEF						
	HEART	LIVER	KIDNEY	TONSIL	LUNG	SPLEEN	BRAIN
	REACTIONS SHOWING AGREEMENT						
7	++++	++++	++++	++++	++++	++++	++++
55	–	–	–	–	–	–	–
	REACTIONS SHOWING VARIATION						
3	++++	++++	++++	++++	++++	++++	+
5	++++	++++	++++	++++	++++	++	++
2	++++	++++	++++	++++	++++	++	–
4	++++	++++	++++	++++	+++	+	+
1	++++	++++	++++	++++	++	–	–
2	++++	++++	++++	++++	++++	–	+
1	++++	++++	++++	++++	++	+++	+
1	++++	++++	++++	+++	+++	++	++
3	++++	++++	+++	+++	+	+	–
1	++++	++++	++++	+	–	–	–
1	++++	++++	++	++	+	–	–
1	++++	++++	++	–	+	–	++
1	++++	++	++++	–	–	–	–
3	++++	+++	–	–	–	–	–
1	++++	++	–	+	–	–	–
1	++++	–	++	–	–	–	–
2	++++	+	+	+	+	+	+
1	++++	+	+	–	–	–	–
1	+++	++	++	++	++	++	++
1	+++	++	+	–	+	–	–
1	++++	–	–	+	–	–	–
1	++++	–	–	–	–	–	–
20	++	–	–	–	–	–	–

CONCLUSION

The antigenic substance responsible for precipitation with syphilitic serum is present in various tissues of the body. The quantity available, however, varies with the tissue. Of seven beef tissues tested; namely, heart, liver, kidney, tonsil, lung, spleen and brain, the largest amount of antigenic substance was found in the extract of heart muscle.

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LABORATORY METHODS

THE BACTERICIDAL ACTION OF WHOLE BLOOD AS DETERMINED BY THE HEIST-LACY METHOD*

By B. S. Parks, M.D., M. Sc., Parkersburg, West Virginia

THE announcement by George D. Heist, Solomon Solis-Cohen and Myer Solis-Cohen, of their method to determine the bactericidal power of whole coagulated blood, has apparently opened a new avenue of approach to the study of certain phases of immunity.

The application of this method has given birth to new and improved methods in the treatment of the diseases due to bacteria and their toxic products.

These investigators described a test by which it is possible to distinguish in vitro between animals that are either susceptible or immune to infection with the pneumococcus. They found the same test applicable in distinguishing between animals that are either immune or susceptible to infection with the globoid bodies, as well as infection with meningococcus and other bacteria.

Heist, Cohen, Kolmer and Matsunami were able to determine the varying degrees of susceptibility to infection by the meningococcus in human beings by this same method.

They were able to measure the gradual increase in the degree of immunity to pneumococcus infection during convalescence from pneumonia.

Many investigations have been made by various workers and some of the more important bacteria, from an etiologic standpoint, were studied and their reaction to whole blood determined.

These investigations have opened up a new avenue of approach to the study of focal infections as a causative factor in the production of disease, and have revealed a new field for study by the scientific investigator and the clinician, which if developed sufficiently, may prove of inestimable value in treatment and prophylaxis. It is obvious that the problem for the clinician is to determine where the foci of infection is located; it remains for the investigator to determine what relation this focus of infection bears to the disease from which the patient is suffering.

The technic of this method has been fully outlined by Heist, Kolmer and Cohen, and I feel that a detailed description would be unnecessary at this time. Heist in elaborating this test made use of the many stemmed pipette of Wright, and availed himself of the suggestion of Prof. Lacy in regard to

*From the medical clinic of Dr. George Morris Piersol, and the laboratories of the Graduate School of Medicine, Dr. John A. Kolmer, director, of the University of Pennsylvania.
Read by invitation at the Fourth Annual Meeting of the American Society of Clinical Pathologists at Philadelphia, May 20-23, 1925.

the principle of capillary attraction in filling the tubes, first with the bacterial culture, then after the removal of the excess of bacterial suspension (sufficient number of bacteria adhering to wall of pipette), the same principle is used in filling the tubes with patient's blood.

The ordinary bacteriologic laboratory technic and care are used in procuring pure, uncontaminated cultures, incubation, staining, etc., to identify the various organisms.

The real point of interest as the end-result of the test is the survival of organisms after the blood is added, and the dilution of the culture which the blood has not destroyed.

Suffice it to say that a careful technic and close observance of the details of the test, are necessary if data of value are to be accumulated.

This method, as is well known, requires the isolation in pure culture of all organisms present. The bactericidal action of the whole blood of the patient is now determined against five dilutions of each organism in a series of capillary tubes, the results being evaluated according to the greatest number of organisms inhibited or destroyed by an equal volume of blood.

In order to further study the method of Heist and the Solis-Cohen in its clinical application and its therapeutic effect, I began the study of a series of cases.

This work was carried out in the laboratory of clinical pathology of the Graduate School of Medicine of the University of Pennsylvania, under the direction of John A. Kolmer.

The cases studied were selected from the dental clinic of David Goodfriend at the Polyclinic hospital, and from cases in the wards of the same hospital and from the service of G. M. Piersol.

They were all cases of focal infection presenting symptoms of many diseases, such as arthritis, corditis, neuritis, frequent sore throats, etc.

Method of Study.—A culture was taken from the infected area by means of a sterile cotton applicator, and streaked upon blood agar plates.

The original streaking was branched by making short lateral strokes across the main streaking so that the colonies would grow separately. In this way one would be enabled to more easily and accurately identify and pick out the colonies of the various organisms, thus procuring a pure culture of each.

The blood agar plates were inoculated for twenty-four hours.

The colonies were then examined both macroscopically and microscopically by smear and stain to identify the various organisms, and when necessary, cultural methods were resorted to in order to make identification positive in the event of existing question in identifying any particular organism.

A pure culture of each organism was procured and bouillon tubes inoculated. Rosenow's media was exclusively used for pure cultures of streptococcus because this media seemed by far the preferable one for this organism. The bouillon tubes and tubes of Rosenow's media were then incubated for twenty-four hours. At the end of the period of incubation the proper dilutions were made for each organism, the many stemmed pipette being used as previously suggested by Heist.

From the organisms which were not destroyed by the patient's blood an autogenous vaccine was prepared in the usual way. I shall report some of the cases studied and a brief history, result of treatment, etc.

CASE 1.—Mrs. V. S., age fifty-seven years, a housekeeper. She has had a generalized arthritis for seven years, with arms, back, and lower limbs stiff, and unable to flex limbs or move any joints of arms, hands or lower limbs. Her hands were swollen, stiff and painful; fingers stiff and swollen. She was unable to turn in bed or to help herself in any way.

Examination showed many infected teeth with apical abscesses. Teeth were extracted, and smear taken and cultured upon blood agar plates, etc.

There were isolated from the culture a pure streptococcus, Staphylococcus aureus and pneumococcus.

A vaccine was prepared from the Staphylococcus aureus, this being the only organism which the patient's blood had not destroyed at the end of twenty-four hours.

Marked and continued improvement resulted from the administration of the vaccine.

CASE 2.—N. D., male, aged fifteen years. The patient had mitral incompetency and mitral stenosis resulting from an attack of endocarditis. The teeth were in poor condition; many apical abscesses and infection about the teeth.

The diseased teeth were extracted. A culture from the teeth which were extracted showed Streptococcus hemoliticus and Staphylococcus aureus.

Upon patient's whole blood there was found surviving the twenty-four-hour incubation period the hemolytic streptococcus, but the Staphylococcus aureus had disappeared.

A vaccine was prepared from the Streptococcus hemoliticus.

No improvement resulted.

CASE 3.—S. S., male, aged twenty-one years, has had enlarged tonsils and frequent attacks of sore throat during the winter for several years. Three years ago the patient developed an otitis media in the left ear, and the drum was perforated. Following the attack of middle ear infection he had his tonsils removed. Since removal of the tonsils three years ago, he has suffered from frequent attacks of pharyngitis accompanied by an offensive breath. During each attack of pharyngitis the lymphatic glands on both sides at the angle of the jaw became enlarged. His condition remained unchanged despite energetic treatment by the usual clinical methods.

A smear and culture from the rhinopharynx showed Streptococcus viridans, Staphylococcus aureus, and Micrococcus tetragenus. Cultures were made upon whole blood, which showed a growth of Streptococcus viridans, but no Staphylococcus aureus or Micrococcus tetragenus.

A vaccine was prepared from the Streptococcus viridans and administered. Since then the patient has had no further recurrence of the pharyngitis.

CASE 4.—A girl, aged sixteen years, came to the clinic complaining of generalized joint involvement. She had a mitral lesion and convulsive seizures, probably epileptic. Her teeth were in bad condition. Three were extracted because of apical abscesses, and a smear from these developed a growth of hemolytic streptococcus, Staphylococcus aureus and pneumococcus.

On patient's blood only the streptococcus survived, from which a vaccine was prepared.

No improvement followed administration of the vaccine.

CASE 5.—E. C., female, aged thirty-eight years, had suffered from neuritis and generalized joint pains for three years, but no stiffness of joints was ever noted by the patient. The x-ray disclosed many dead and infected teeth. These were extracted. A smear taken from the root of an extracted tooth showed a pure culture of Streptococcus viridans, but no other organisms were found.

On patient's blood the Streptococcus viridans grew and from it a vaccine was prepared.

The patient's condition was much improved by use of the vaccine.

CASE 6.—N. D., male, aged twenty-six years, had suffered from attacks of rheumatism for seven years, but had no stiffness of joints or contractures. He has mitral regurgitation.

At present, his joints are painful and tender. The teeth were examined and several apical foci located. These teeth were extracted, and a smear and culture made which showed a growth of nonhemolitic streptococcus and Staphylococcus aureus.

Upon patient's blood there was a growth of streptococcus, but the staphylococcus failed to grow.

A vaccine was prepared from the streptococcus.

Patient steadily improving since vaccine administration was instituted.

CASE 7.—Mrs. L. W., age forty-six years, complained of pains in joints, muscular stiffness, and soreness. She has had frequent attacks of acute rheumatic arthritis which confined her to bed for variable lengths of time on various occasions.

Teeth examined and many apical foci detected.

Diseased teeth extracted. Culture showed only a growth of hemolytic streptococci, which grew upon patient's blood. A vaccine was prepared from the streptococcus and administered. No improvement resulted.

At present the patient is being treated in the clinic for a cholecystitis which may be an etiologic factor in causation of continuation of symptoms.

CASE 8.—R. P., colored, male, age thirty-five years, has had frequent attacks of rheumatism for ten years. During the last four months he has been incapacitated for work because of pain in his back and joints.

Several abscessed teeth were found by x-ray. These were extracted and smears taken. Culture showed growth of streptococcus and Staphylococcus aureus.

On patient's blood the streptococcus grew well, but no growth of Staphylococcus aureus appeared.

A vaccine was prepared from the streptococcus, and patient has steadily improved since beginning its use.

CASE 9.—H. N., male aged twenty-five years, came to the clinic complaining of pains in the joints, muscular soreness, and pain in the lumbar muscles. He has had these acute attacks during the winter months for the past three years. Apical foci of infection detected and the diseased teeth were extracted. A smear was taken and upon culture showed a growth of the Streptococcus viridans and a few Staphylococcus aureus.

Upon the blood only the Streptococcus viridans grew, and from this organism a vaccine was prepared.

No improvement has been noted in the patient's condition so far.

CASE 10.—L. G., male, aged thirty-three years, had myocarditis following influenza. He has had frequent attacks of sore throat during the winter months for five years. A culture from the tonsil and rhinopharynx showed Streptococcus viridans and Staphylococcus aureus.

On patient's blood only the Streptococcus viridans grew, and from this a vaccine was prepared.

Patient has steadily improved since beginning vaccine treatment.

No specific conclusions can be drawn as to the therapeutic efficiency of this method from the limited number of cases that have been studied. As previously stated elsewhere, a comparison of results in a larger series of cases is necessary in order to arrive at any definite conclusions.

It was found not only from the above cited cases, but in numerous cases not cited here (because for various reasons they could not be followed up), that in nearly all cases where the streptococcus was isolated, this organism grew upon the patient's blood. This occurred in nine of the above cases,

while in only one case did it grow upon culture and not upon the patient's blood, and this was probably due to a fault in the technic.

The findings in the unreported cases studied in the laboratory also warrant this statement.

If the streptococcus is the causative agent in these cases, then it must produce the multiplicity of symptoms by its toxins. For, clinically, we know that a streptococcus bacteriemia is a more serious condition than was encountered in our cases. Again, it is difficult to believe that the nondestructive lesions of rheumatic arthritis and the destructive lesions of Streptococcus endocarditis are caused by the same organism.

If this organism were free in the blood stream in both cases, how could it produce such divergent lesions?

At present, we do not know the immediate cause of the joint symptoms in rheumatic arthritis, but since the function of the joint is not destroyed, it is difficult to attribute the lesion to the streptococcus. We would be more inclined to attribute the lesions to some bacterial toxin than to the bacteria themselves. The toxins may be absorbed from a local foci, or from a toxin derived from the destruction by the blood of bacteria reaching the blood stream from such local foci of infection, and the continued invasion of the blood stream by bacteria or their products should and probably does, increase the patient's resistance to such bacteria.

If this is true, we would expect the blood to possess sufficient bactericidal power to prevent the growth of such organisms in it. On the other hand, in a foci of infection we often isolate the streptococcus with other organisms and the streptococcus grows upon patient's blood, while the others do not.

May we not well reason that the organisms which have been reaching the blood stream have caused the patient to develop such a degree of immunity against this organism that his blood is bactericidal to it; and that the organism growing on the blood is harmless in so far as its having been entering the blood stream is concerned?

Consequently the bactericidal power of the blood has not developed against this specific organism.

CONCLUSIONS

From observation and study of this problem it is believed that the following conclusions are at present justified.

1. The whole coagulable blood of man may possess the property of destroying or inhibiting the growth of certain pathogenic bacteria.

2. Bacteria which will not grow in the whole blood in vitro but are destroyed by it, are probably incapable of producing a bacteriemia.

3. Bacteria which will grow in the whole coagulable blood in vitro are probably capable, if they reach the blood stream, of producing a bacteriemia.

4. Bacteria which will not grow in the whole coagulable blood of a patient in vitro may still produce a localized infection with the production of symptoms due to toxins and other bacterial products absorbed from such lesions with the production of symptoms.

5. Bacteria from a local infection capable of growing in the patient's blood in vitro may not be the cause of the disease, although potentially capa-

ble of infecting the blood, until this tissue acquires bactericidal properties by immunologic processes.

6. Autogenous vaccines prepared of bacteria from localized infections weeded out by this method are not necessarily specific although therapeutic results may be secured by nonspecific protein reactions.

7. Until further study has been made and more data accumulated, this method is worthy of further study and especially in relation to the perplexing problem of deciding which organism in a mixed localized infection should be incorporated into autogenous vaccines.

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THE VALUE OF ACETONE DETERMINATION IN EXPIRED AIR IN CORRELATION WITH ALVEOLAR CARBON DIOXIDE TENSION*

Practical Methods, Technic, and Apparatus

By Paul Roth, M.D., Battle Creek, Mich.

THE value of carbon dioxide determinations in alveolar air and a simple test for acetone in the expired air were brought to my attention during a period of study of the respiratory exchange and methods of estimation at the Carnegie Nutrition Laboratory, in Boston, in 1912 and 1913. H. L. Higgins, then a member of the staff of that institution, was carrying on, under the direction of F. G. Benedict, various observations in connection with extensive experimental studies being made there on diabetes. The laboratory procedures used and perfected by Higgins[1] promised to be of clinical value and were at once introduced at the Battle Creek Sanitarium for purposes of diagnosis and as therapeutic guides in diabetes. They soon gained the favor of members of the staff as a means of detecting and measuring the degree of acidosis, not only in diabetes but in various other conditions. At the request, especially of C. E. Stewart, then chief of the diabetic service, these tests were about a year later included in the list of routine examinations to which all the patients are subjected and methods then used[2] were later modified[3]; the latest improvements being now published for the first time.

The preference is still given to these gasometric methods because they are as yet the only ones which are simple enough and sufficiently reliable to be practical for the wide and frequent use to which they are put. Direct observations upon the blood by the methods of Van Slyke[4]; Cullen[5]; Myers, Schmitz and Booher[6] are resorted to only in selected cases. A test for acetone in the expired air has been from the start routinely done simultaneously with the determination of the alveolar CO_2 tension.

During the first few years after the introduction of these tests, at a time when the management of diabetes was far from being as efficient as it is today, severe acidosis was frequently observed and fatal diabetic coma was not of rare occurrence.

The clinical application of these tests further showed that acetone occurs very frequently in disease and readily appears even in normal individuals from as slight a provocation as missing a meal or two. Needless to say that the presence of acetone has the same significance whether found in the expired air, where it is most easily detected, or in the blood or urine. It is invariably associated with acidosis of ketonic origin. Its absence when acidosis is present, therefore, indicates that the acidosis is due to entirely different

*From the Metabolism Laboratory of the Battle Creek Sanitarium, Battle Creek, Mich. Read before the Fourth Annual Convention of the American Society of Clinical Pathologists, in Philadelphia, May 20-23, 1925.

causes such as those associated with or due to renal insufficiency. This is the so-called "phosphatic type" of acidosis. These two types of acidosis often coexist; therefore, the occurrence of acetone does not rule out the possibility of a phosphatic type of acidosis being also present.

Acidosis can readily be detected by the various simple and well-known procedures which are to be found in any up-to-date textbook of physiology and of physiologic chemistry. It so frequently occurs in disease that the clinician will find it well worth while to systematically look for it in both acute and chronic affections. The dangers of severe acidosis are in general fully recognized, but when it is of moderate intensity its significance and

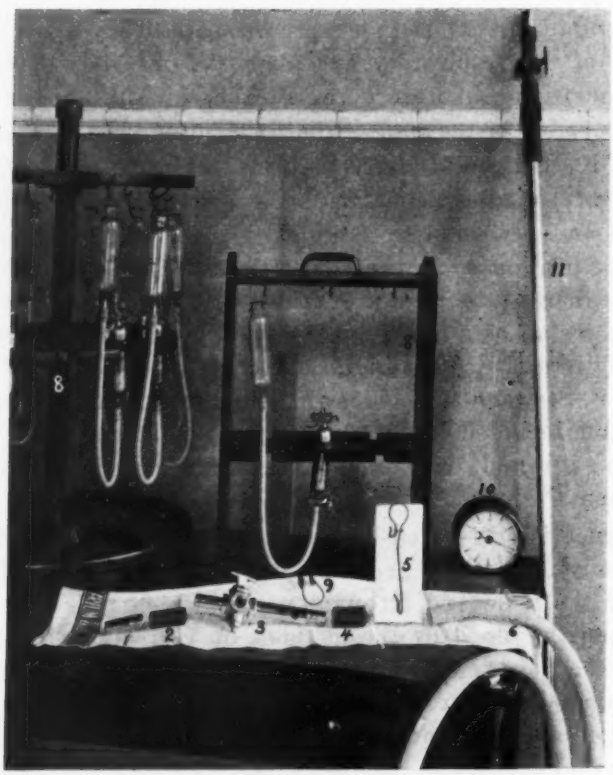

Fig. 1.—Equipment for obtaining a sample of alveolar air by the author's method. Disassembled parts from a previous paper[8] which gives a detailed description of each of the numbered parts. A ⅝ inch three-way cock is now used.

bearing should not be lost sight of. The clinician who is interested in the border line of disease and in preventive medicine will find this field of investigation of fundamental importance.

The normal metabolic processes throughout the body are dependent upon remarkably close fundamental biologic conditions. Even a slight departure from these means disaster which is efficiently averted by delicate and complex mechanisms. One of these mechanisms is that which regulates the reaction or ionization of the body fluids.[7] Whenever we find that such a mechanism has become persistently inadequate, the danger signal should be heeded, because any departure from the normal is the stepping-stone for

metabolic disturbances of various sorts. Vital energy is depressed, repair and recovery are retarded, senescence is hastened,—in fact, both acidosis and alkalosis are incompatible with life and health. Subjects with acidosis, as is well known, are poor surgical risks. In an unpublished review of the alveolar CO_2 tension in 260 consecutive major surgical operations performed at the Battle Creek Sanitarium, eight to ten years ago, 174 (67 per cent) showed a CO_2 tension below the minimum normal before operation. While the death rate, less than twenty days after the operation, amounted to 11 per cent of these cases, there was a mortality of only 0.5 per cent among those who showed a normal CO_2 tension before the operation. These figures at least show that acidosis adds a material risk in surgical cases.

The frequency of acidosis in general clinical cases was well shown in a simultaneous review of 2,305 consecutive cases. A conservative estimate

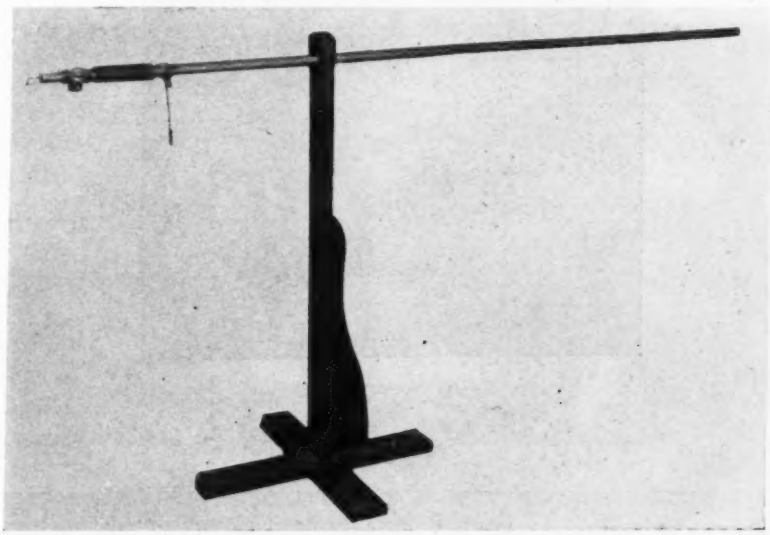

Fig. 2.—Collecting tube (5 ft. long, ¾ inch, capacity about 500 c.c.) with support.

showed that 44 per cent of these cases gave an alveolar CO_2 tension below 37 mm. Severe acidosis was observed in about 10 per cent of the total number.

Alkalosis is of late attracting the attention that it deserves and much of what has just been said about acidosis applies also to alkalosis. This shifting of the "acid-base" balance toward the alkaline side is very ably discussed in a recent paper by Kast, Myers and Schmitz.[8] With this same paper a very well selected list of references to the literature on the subject is given.

The present study was undertaken with the full expectation that a careful investigation of a large number of cases would confirm the observations casually made a few years ago. The diagnosis and the laboratory findings of one thousand cases, taken at random from the records of the past three years, were tabulated. In every case the diagnosis was confirmed by urinalysis, blood chemistry, alveolar CO_2 tension, and acetone in the expired air. These tests were performed on the same day with but few exceptions,

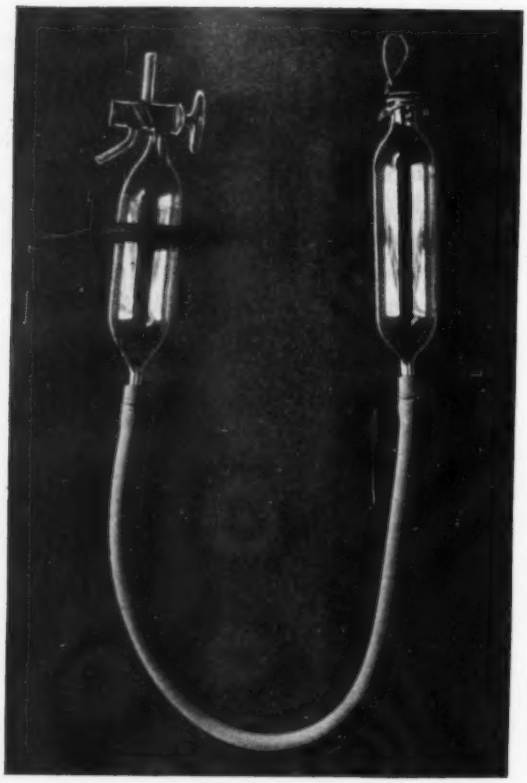

Fig. 3.—Collecting burette unit.

Fig. 4.—Collecting tube with burette in place. The burette is filled with mercury to the very tip, which is inserted through a small opening in the rubber sleeve.

and then none over three days apart. The accompanying table presents the most striking points observed which fall within the scope of this paper. The cases were classed under the following heads:

1. *Diabetics (210 cases).*—In this group were placed only those diabetics who did not show any renal involvement; no albumin, no casts in the urine, a blood nonprotein nitrogen not over 34.0 and blood uric acid not over 5 mg. per 100 c.c. A very few showing an amount of uric acid above the normal without any other evidence of renal insufficiency were also included in this group. These diabetics were all of the moderate type.

2. *Diabetic-Renal (221 cases).*—Representing all degrees of diabetes with definite signs of renal involvement.

3. *Renal (242 cases).*—Including all cases with renal involvement without any signs of diabetes.

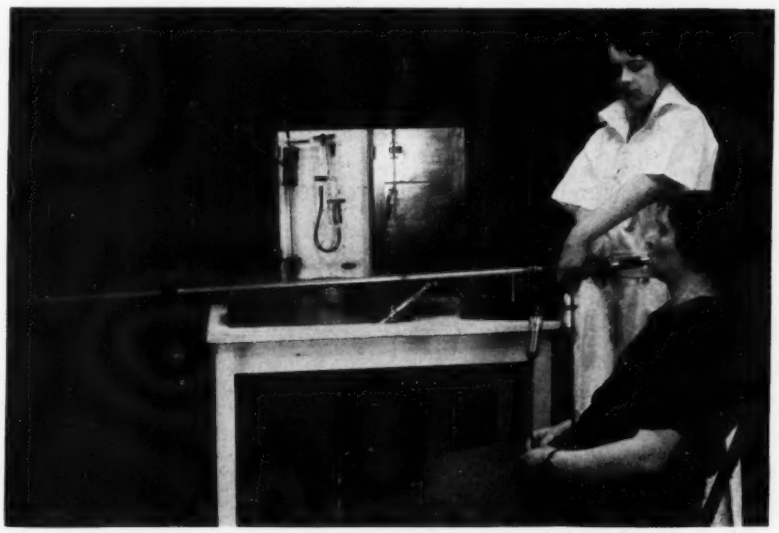

Fig. 5.—Collecting alveolar air after 20 seconds, rebreathing through the 5 foot tube. The nose should be clamped.

4. *Others (500 cases).*—Showing no renal involvement or any diabetic taint.

Each class is divided into two groups.

A. *No Acetone.*—Cases having shown no acetone in the expired air either at the entrance examination test or in any subsequent tests.

B. *With Acetone.*—Cases having shown acetone in the expired air one or more times.

The alveolar CO_2 tension recorded under each group is divided into four ranges:

1. The Normal, with tensions of 40 mm. or over.
2. Mild acidosis " " 35 to 39 mm.
3. Moderate " " " 30 to 34 mm.
4. Severe " " " 29 mm. or less.

TABLE I

THE ALVEOLAR-CO_2 TENSION IN THE PRESENCE OR ABSENCE OF ACETONE IN EXPIRED AIR

(1000 cases, years 1923 and 1924.)

Their relative occurrence in: (1) Diabetes without renal involvement (2) Diabetes with renal involvement (3) Renal cases without diabetes (4) Other cases with no renal or diabetic symptoms.

ALV. CO_2 TENSION MM.	1. DIABETES 36%		2. DIABETIC-RENAL 40%		3. RENAL 69%		4. OTHERS 71%	
	Cases	%	Cases	%	Cases	%	Cases	%
Without Acetone								
40 - 50	15	33	23	36	54	37	121	37
35 - 39	28	61	32	50	72	49	181	55
30 - 34	3	6	9	14	17	12	24	7
29 or less	0	0	0	0	3	2	4	1
With Acetone	64%		60%		31%		29%	
40 - 50	25	31	27	28	20	31	52	31
35 - 39	47	57	59	61	30	46	94	55
30 - 34	10	12	9	9	11	17	23	13.5
29 or less	0	0	2	2	4	6	1	.5

Tensions between 30 and 39 mm. are included under two separate ranges merely because of the great difference of frequency observed in these two ranges.

The chief facts which this table shows are as follows:

1. Acetone occurs in the expired air twice as frequently in diabetics (64 per cent) and in the diabetic-renal (60 per cent) as in exclusively renal (31 per cent) and "other" cases (29 per cent).

2. The relative number of cases with a normal CO_2 tension is practically the same in all four groups whether acetone is present or not.

3. Mild acidosis is slightly more frequent in the diabetics (59 per cent) and diabetic-renal (56 per cent) than in the renal (48 per cent) and other cases (55 per cent).

4. Moderate acidosis is slightly more frequent in renal cases (13 per cent) and in diabetic-renal (11 per cent) than in diabetics (10 per cent) and other cases (9.5 per cent).

5. Severe acidosis occurred more frequently in renal cases (3.5 per cent) and in other cases (1 per cent) than in diabetics (only 0.7 per cent). (In a series of 36 diabetics examined previous to 1920, severe acidosis occurred in 11 per cent of the cases.)

6. Severe acidosis was not observed in the group of 128 consecutive cases of diabetes whether acetone was present or not.

7. Severe acidosis was likewise not found in the group of 146 diabetic-renal cases without acetone.

8. Severe acidosis occurred in only 2 per cent of the diabetic-renal cases with acetone. (In a series of 40 diabetic-renal cases with acetone examined previous to 1920, severe acidosis occurred in 7.5 per cent of the cases.)

The reader will find in the references to the literature given here, complete descriptions of the methods referred to in this paper.

Figs. 1 to 8 present my modifications and improved methods for collect-

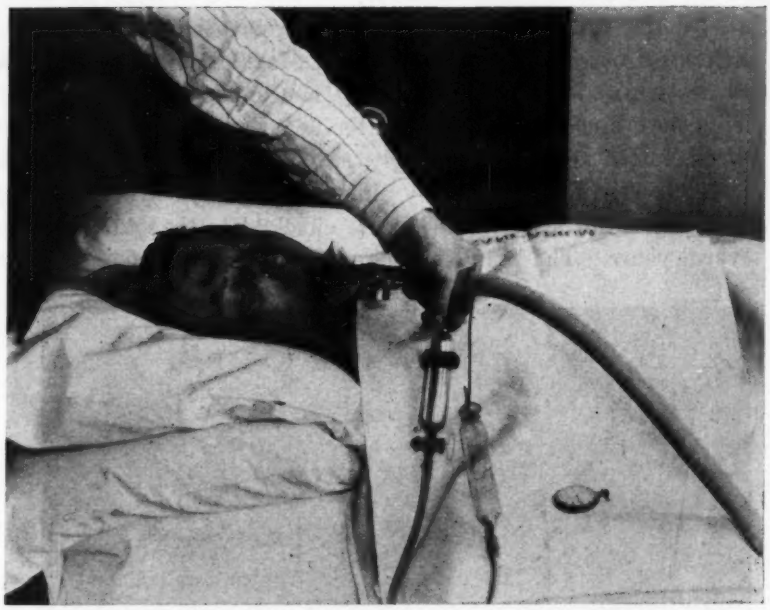

Fig. 6.—Collecting alveolar air (as in Fig. 5) using a 5 foot ¾ inch rubber tube. Subject in bed.

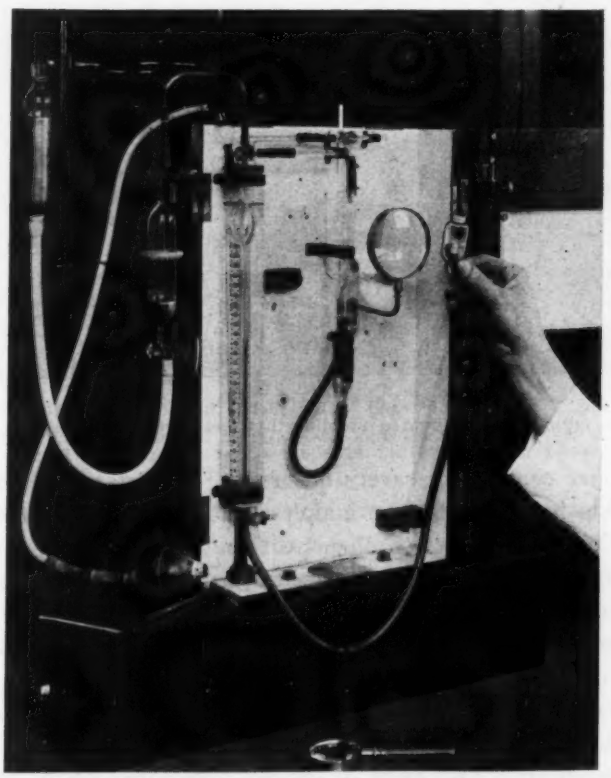

Fig. 7.—A Haldane Air Analysis Apparatus modified for CO_2 analysis only. Sampling burette in place.

ing alveolar air and for the determination of the CO_2 tension by analysis of the sample with the Haldane[9] or Henderson[10] apparatus.

Figs. 8 to 16 illustrate the application of Marriott's method for alveolar CO_2 tension determination.[11] Although my method is generally used on account of being both speedier and of greater accuracy, Marriott's method has for years been found to be exceedingly satisfactory and most reliable for bedside use. The results obtained by this method have systematically been compared and the solutions and standards checked by repeated analyses for the past several years. The results checked usually within 1 or 2 per cent; a

Fig. 8.—Same as Fig. 7 with a shortened water jacket intended to protect the bulbs of the burettes only. The graduated stem is thus better exposed for reading.

difference of 3 per cent being rarely observed. The standards are now very permanent. I am informed by the makers that a suitable mask and a three-way cock will be furnished with the outfit on request.

The football bladder with an enlarged opening (Fig. 11) presents the advantage of being self-inflating and does not require the use of a hand bulb.

Figs. 17 and 18 show my simple tube for the detection of acetone in the expired air using Scott-Wilson solution.

Test for Acetone in Expired Air.—The subject is asked to take a moderate breath and to expel it completely through 2 or 3 c.c. of Scott-Wilson solution (see below) placed in a test tube or in my apparatus (Fig. 18). The test is reported negative if the solution remains perfectly clear after three or

four moderate breaths have been expelled through the solution. A pearly opalescent clouding or precipitate is due to acetone, the amount of which is expressed as trace, plus, double plus, etc.

Scott-Wilson solution[12].—To 10 gm. of mercuric cyanide dissolved in 600 c.c. of water add a cooled solution of 180 gm. of sodium hydroxide in 600 c.c. of water. Transfer this mixture to a heavy walled jar, and to it add 2.9 gm. of silver nitrate dissolved in 400 c.c. of water. The silver solution should be added in a slow stream, and the addition must be accompanied by constant and vigorous stirring with a glass rod. If properly made, the silver dissolves

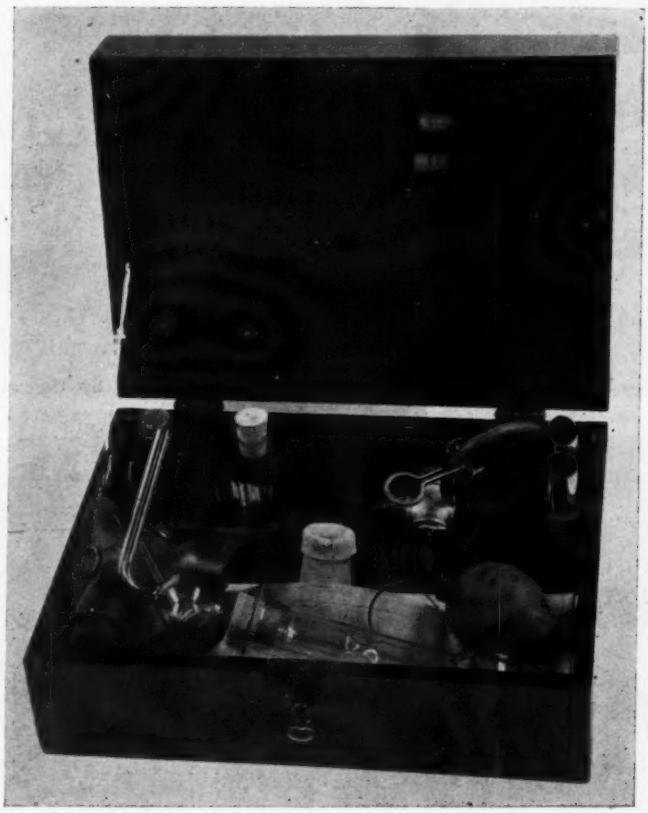

Fig. 9.—Outfit for the collection of alveolar air and the determination of the CO_2 tension (Marriott Method) and acetone in the expired air (Roth).

completely, giving a clear solution which is at once available for use. If the solution is turbid, it should be set aside to settle for three or four days and the clear supernatant liquid removed by means of a siphon.

In the clear reagent a new sediment gradually forms, so that the solution deteriorates slowly, and after a few months is not serviceable for quantitative work, though still good for qualitative tests.

DISCUSSION

It must be borne in mind that the diabetics and other cases treated at the Battle Creek Sanitarium are not likely to come from a medically neglected

class of patients. On the whole they are more likely to have had, before coming to this institution, better and more modern medical care than is generally found. Therefore, the occurrence of severe acidosis would unques-

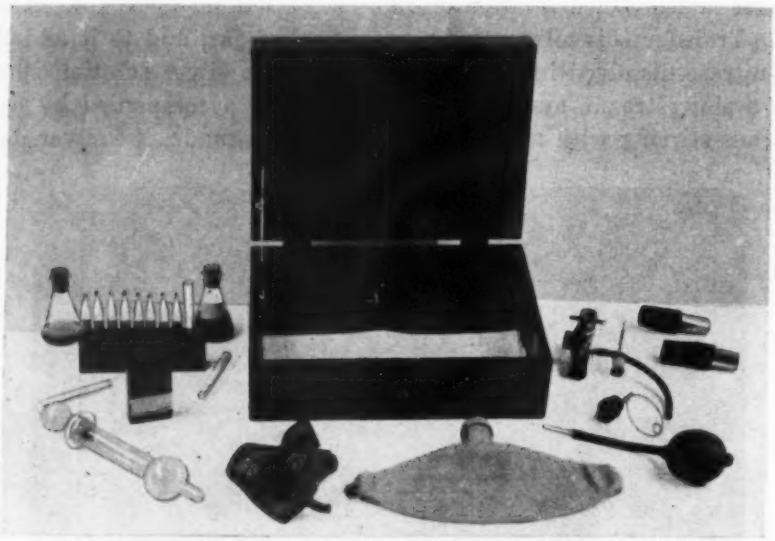

Fig. 10.—Marriott alveolar CO_2 tension outfit, as modified by the writer.

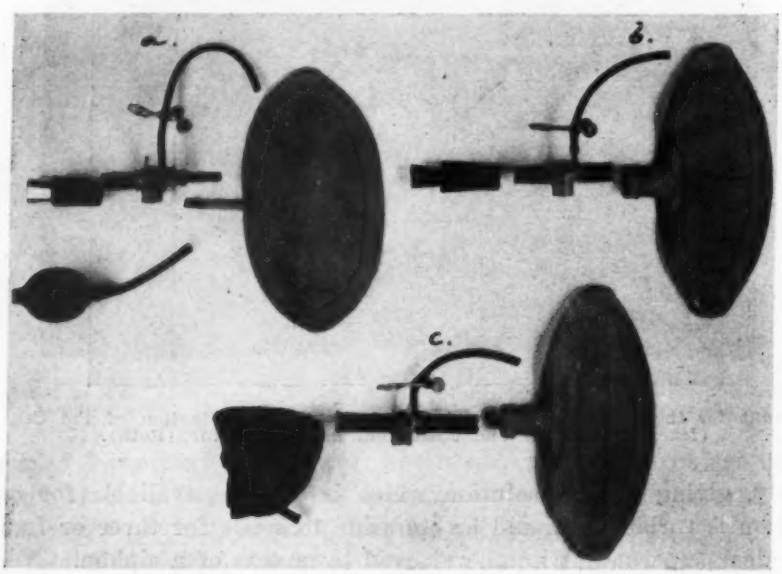

Fig. 11.—Three types of collecting units. (*a*) Using an ordinary football bladder. Requires a rubber bulb for inflation. (*b*) Bladder with ¾ inch opening. Practically self inflating. (*c*) Same with mask in place of mouthpiece.

tionably be relatively lower than in cases generally admitted in hospitals. Severe acidosis is nowadays very rarely encountered in the class of cases referred to above. There is very little question about this being the result of a general better understanding of the proper treatment of this disease. The

use of insulin is no doubt bearing splendid results but is not wholly responsible for them. No clinician can continue to remain unacquainted with the best and indispensable dietetic measures the moment the use of insulin

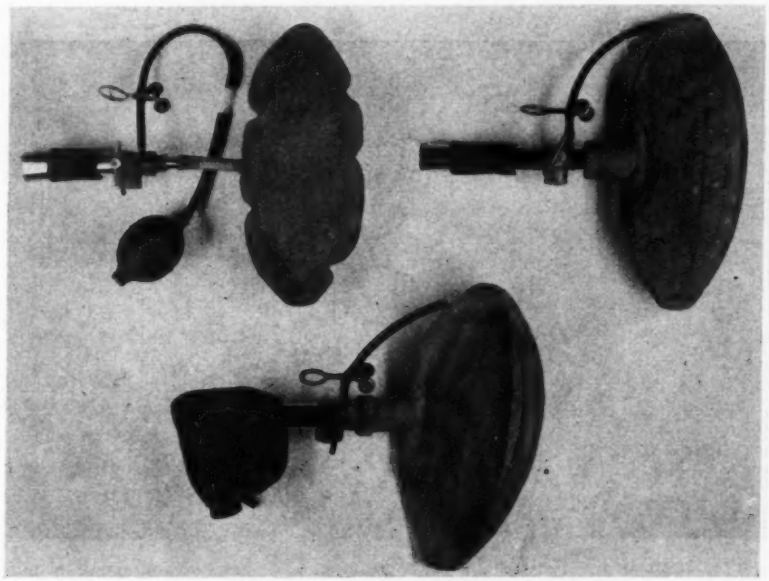

Fig. 12.—Same as Fig. 11, collecting units assembled.

Fig. 13.—Collecting alveolar air for CO_2 tension determination, using a mouthpiece.

is considered. With the high fat and more especially with the high protein diet generally advocated in diabetes until quite recently, acidosis was strongly encouraged and difficult if not impossible to control.

C. C. Hubly, who for a number of years has been chief of the diabetic service and through whose kindness I have had access to the records of his most efficient work, informs me that the number of undiagnosed cases of diabetes has considerably decreased in recent years. Acidosis is more suc-

Fig. 14.—Collecting alveolar air for CO_2 tension determination, using a mask.

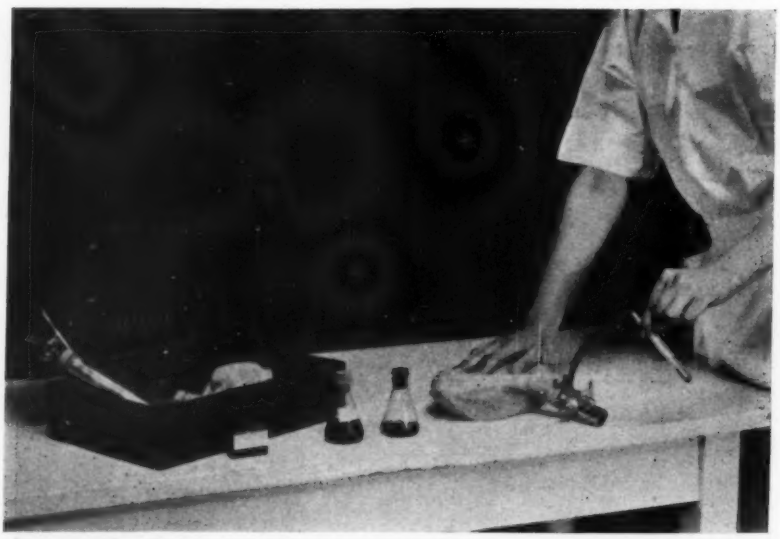

Fig. 15.—Expelling alveolar air and bubbling it through the standard bicarbonate solution with indicator "phenolsulphonephthalein" in test tube. (Marriott.)

cessfully treated when it is of the ketonic type alone and it is indicated by the presence of acetone in the urine or in the expired air. Proper dietetic and other therapeutic measures very quickly cause a disappearance of the acetone and a return of the alveolar CO_2 tension to the normal in the cases uncomplicated with renal involvement. The disappearance of acetone with a CO_2 tension below the normal must mean that while the ketonic acidosis is completely

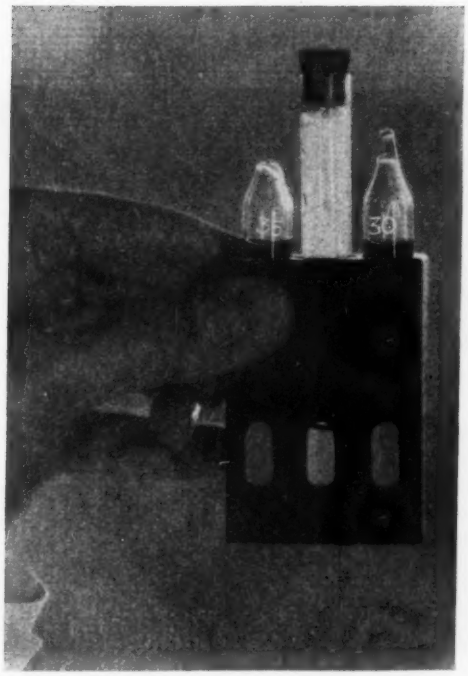

Fig. 16.—Colorimetric estimation of CO_2 tension. Comparing the unknown with marked standards. (Marriott.)

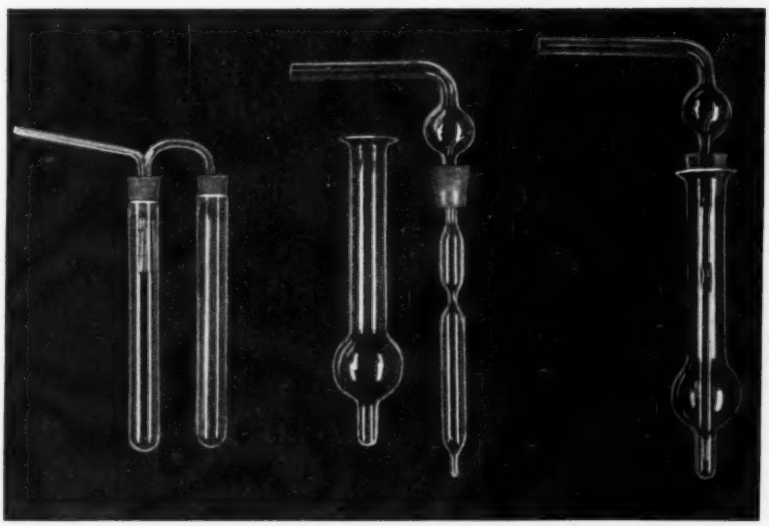

Fig. 17.—Left, test tube unit for detecting acetone in the expired air. Center, safety detector of acetone in expired air (Roth). Right, the same assembled. The tip end of the external tube only is filled with "Scott-Wilson" solution.

held in check, an acidosis due to renal insufficiency is still present. It seems that an acidosis of renal origin is more difficult to control and to eradicate. This is shown by the fact that not infrequently the well-managed cases of diabetes can readily be kept acetone-free in spite of the persistence of a more

Fig 18.—Safety acetone detector, as used. (Roth.)

or less pronounced acidosis. The treatment of this type of acidosis is as yet poorly understood.

I am greatly indebted to my colleagues, C. C. Hubly and W. B. Lewis, chief chemist, for their helpful cooperation and suggestions in this study.

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(*For discussion, see page* 295.)

STUDIES IN LOCAL ANESTHESIA. III*

The Pharmacology of Some Para-Amino-Benzoate Compounds

Türck's Reflex Method in the Determination of Local Anesthesia

By W. J. R. Heinekamp, M.S., M.D., Chicago, Ill.

THE method used is based on Türck's method of recording reflex time. The frog's leg is placed about midway to the knee in a solution of the anesthetic for ten consecutive minutes and the effect determined at definite intervals by immersing the foot in tenth-normal HCl. If anesthesia was produced, the foot was not withdrawn from the acid solution. If anesthesia had not been produced, the foot was withdrawn.

Protocol 1.—

1 per cent Cocaine Hydrochloride

Frog		
I	Right leg	10 min.
	Left leg	10 min.
II	Right leg	10 min.
	Left leg	10 min.
III	Right leg	10 min.
	Left leg	10 min.

Protocol 2.—

A. I.

Frog				
I	Right leg	No anesthesia	1 hr.	
	Left leg	"	"	"
II	Right leg	"	"	"
	Left leg	"	"	"
III	Right leg	"	"	"
	Left leg	"	"	"

Protocol 3.—

A. II.

Frog				
I	Right leg	No anesthesia	1 hr.	
	Left leg	"	"	"
II	Right leg	"	"	"
	Left leg	"	"	"
III	Right leg	"	"	"
	Left leg	"	"	"

Protocol 4.—

A. III.

Frog		Anesthesia
I	Right leg	10 min.
	Left leg	10 min.
II	Right leg	10 min.
	Left leg	10 min.
III	Right leg	10 min.
	Left leg	10 min.
		Average 10 min.

*From the University of Illinois, College of Medicine, Chicago.

Protocol 5.—

A. IV.

Frog		Anesthesia
I	Right leg	15 min.
	Left leg	15 min.
II	Right leg	10 min.
	Left leg	10 min.
III	Right leg	10 min.
	Left leg	15 min.
		Average 12.5 min.

Protocol 6.—

A. V.

Frog		Anesthesia
I	Right leg	30 min.
	Left leg	35 min.
II	Right leg	30 min.
	Left leg	20 min.
III	Right leg	30 min.
	Left leg	20 min.
		Average 27.5 min.

Protocol 7.—

A. VI.

Frog		Anesthesia
I	Right leg	30 min.
	Left leg	50 min.
II	Right leg	30 min.
	Left leg	40 min.
III	Right leg	30 min.
	Left leg	30 min.
		Average 35 min.

Protocol 8.—

A. VII.

Frog		Anesthesia
I	Right leg	15 min.
	Left leg	20 min.
II	Right leg	25 min.
	Left leg	15 min.
III	Right leg	15 min.
	Left leg	15 min.
		Average 17.5 min.

Protocol 9.—

B. I.

Frog		
I	Right leg	No anesthesia 1 hr.
	Left leg	" " "
II	Right leg	" " "
	Left leg	" " "
III	Right leg	" " "
	Left leg	" " "

Reflex active at end of hour.

Protocol 10.—

B. II.

Frog	Conditions as with Cocaine.	
I	Right leg	10 min.
	Left leg	15 min.
II	Right leg	20 min.
	Left leg	20 min.
III	Right leg	15 min.
	Left leg	20 min.
		Average 15 min.

Protocol 11.—
B. III.

Frog.	Milky fluid.	
I	Anesthesia	60 min.
II	Anesthesia	50 min.
III	Anesthesia	50 min.

Reflex brisk at 1 hour.

Protocol 12.—
B. IV.

Frog		
I	Right leg	10 min.
	Left leg	10 min.
II	Right leg	10 min.
	Left leg	10 min.
III	Right leg	10 min.
	Left leg	10 min.
	Average	10 min.

No anesthesia at 5 min.

Protocol 13.—
B. V.

Frog		
I	Right leg	10 min.
	Left leg	15 min.
II	Right leg	15 min.
	Left leg	10 min.
III	Right leg	10 min.
	Left leg	10 min.
	Average	11.6 min.

Protocol 14.—
B. VI.

Frog		
I	Right leg	15 min.
	Left leg	10 min.
II	Right leg	10 min.
	Left leg	10 min.
III	Right leg	10 min.
	Left leg	15 min.
	Average	11.6 min.

Tables I and II summarize the protocols.

TABLE I

NO.	NAME	ONSET OF ANESTHESIA
	Cocaine 1%	10 min.
	Novocaine 1%	No anesthesia in 1 hr.
A. 1	Di-methylamino methyl para-amino-benzoate	" " " "
A. 2	Di-ethylamino ethyl para-amino-benzoate	" " " "
A. 3	Di-normal propylamino ethyl para-amino-benzoate	10 min.
A. 4	Di-normal butylamino ethyl para-amino-benzoate	12.5 "
A. 5	Di-isopropylamino ethyl para-amino-benzoate	27.5 "
A. 6	Di-isobutylamino ethyl para-amino-benzoate	35 "
A. 7	Di-secondary butylamino ethyl para-amino-benzoate	17.5 "
B. 1	Di-ethylamino propyl para-amino-benzoate	No anesthesia in 1 hr.
B. 2	Di-isopropylamino propyl para-amino-benzoate	15 min.
B. 3	Di-nor.-propylamino propyl para-amino-benzoate	53.3 "
B. 4	Di-nor.-butylamino propyl para-amino-benzoate	10 "
B. 5	Di-isosecondary butylamino propyl para-amino-benzoate	11.6 "
B. 6	Di-isobutylamino propyl para-amino-benzoate	11.6 "

Designating ten minutes the time necessary for 1 per cent cocaine HCl to totally inhibit a reflex with tenth-normal HCl used as a stimulus as unity, the drugs in molecular concentration corresponding to 1 per cent cocaine HCl have the following comparative values shown in Table II.

TABLE II

NO.	NAME	VALUE
	Cocaine HCl	1.
A. 3	Di-normal propylamino ethyl para-amino-benzoate	1.
B. 4	Di-normal butylamino propyl para-amino-benzoate	1.
B. 6	Di-isobutylamino propyl para-amino-benzoate	0.86
B. 5	Di-iso-secondary butylamino propyl para-amino-benzoate	0.86
A. 4	Di-normal butylamino ethyl para-amino-benzoate	0.80
B. 2	Di-isopropylamino propyl para-amino-benzoate	0.66
A. 7	Di-secondary butylamino ethyl para-amino-benzoate	0.57
A. 5	Di-isopropylamino ethyl para-amino-benzoate	0.37
A. 6	Di-isobutylamino ethyl para-amino-benzoate	0.28
B. 3	Di-normal propylamino propyl para-amino-benzoate	0.188
A. 1	Di-methylamino methyl para-amino-benzoate	0.00
A. 2	Di-ethylamino ethyl para-amino-benzoate	0.00
B. 1	Di-ethylamino propyl para-amino-benzoate	0.00

DISCUSSION

It is seen from Tables I and II that this method does not lend itself to the standardization of local anesthetics. The comparative value as determined by this means, differs considerably from that obtained from more reliable methods.

However, as a general rule the greater the molecular weight of the compound the higher the comparative anesthetic value, as determined by this procedure. While this same conclusion may be drawn from the results obtained by other methods, the exceptions which are present in these results weaken the value of any inferences.

A few of the drugs are markedly irritating and hence it is quite impossible to determine when anesthesia is present, since the foot is withdrawn immediately from the solution, and, hence, a false reflex may alter the end-point ten minutes or more.

This method indicated the power of a drug to produce surface anesthesia, and hence such substances as novacine and apothesine are inactive when tried by this method, although when injected, they are excellent local anesthetics. This method offers corroborative evidence only, and should not be used alone to determine the efficiency of a drug.

THE STANDARDIZATION OF SOME NEW LOCAL ANESTHETICS BY THE PITTINGER METHOD

BY G. W. MOXON, B.S., AND O. V. PAWLISCH, B.S., CHICAGO

IN these experiments we used the method developed by Pittinger, which we believe affords a satisfactory criterion of the efficiency of an anesthetic.

The method is as follows: The hair was clipped and shaved from a dog's back, and an area approximately one inch square marked out. The solution (always 1 c.c. and containing varying amounts of the anesthetic) was injected under the skin in the center of this area.

At the end of five minutes the center of the area was touched with an iron rod (3 mm. in diameter) heated to red heat. If the animal showed signs of irritation or pain, the area was still sensitive, and if not, anesthesia had been secured.

The results are as follows:

A-2-Novocaine Weight milligrams	*Results*
0.005	Sensitive
0.007	Sensitive
0.010	Anesthetic
A-3	
0.005	Sensitive
0.007	Anesthetic
0.010	Anesthetic
A-4	
0.010	Sensitive
0.015	Sensitive
0.017	Anesthetic
A-5	
0.010	Sensitive
0.0125	Sensitive
0.015	Anesthetic
A-6	
0.010	Sensitive
0.010	Sensitive
0.0125	Anesthetic
A-7	
0.005	Sensitive
0.007	Anesthetic
0.010	Anesthetic
B-1	
0.010	Sensitive
0.015	Sensitive
0.020	Anesthetic
B-2	
0.010	Sensitive
0.012	Sensitive
0.015	Anesthetic
B-3 Exp. I.	
0.010	Sensitive
0.017	Sensitive
0.020	Anesthetic
B-3 Exp. II.	
0.015	Sensitive
0.017	Anesthetic
0.020	Anesthetic
B-4	
0.00125	Sensitive
0.0025	Anesthetic
B-5	
0.010	Sensitive
0.015	Sensitive
0.017	Anesthetic
B-6 Exp. I.	
0.020	Sensitive
0.0225	Sensitive
0.025	Anesthetic
B-6 Exp. II.	
0.010	Sensitive
0.015	Sensitive
0.017	Anesthetic

RECAPITULATION SERIES

MINIMUM TO PRODUCE ANESTHESIA

A-2	10 mg.
A-3	7 mg.
A-4	17 mg.
A-5	15 mg.
A-6	12.5 mg.
A-7	7 mg.

MINIMUM FOR ANESTHESIA

B-1	20 mg.
B-2	15 mg
B-3	18.5 mg.
B-4	2.5 mg.
B-5	17 mg.
B-6	21 mg.

CONCLUSION

This is a comparatively simple, accurate, and efficient method of standardizing the local anesthetics. When used in this way, the results coincide closely with those obtained by other methods.

This method shows that *A-3* and *B-4* are especially valuable and deserve consideration as local anesthetics for general use. They are more efficient than procaine, but slightly more toxic. Since less of the drug is required to produce the anesthetic effect, toxicity is the same as procaine with *A-3,* and less with *B-4,* which is four times as active while only twice as toxic.

COMMUNICATION

Editor, JOURNAL OF LABORATORY AND CLINICAL MEDICINE,

Dear Sir:

In the July, 1925, number of the JOURNAL OF LABORATORY AND CLINICAL MEDICINE the writer published a paper on a complement-fixation test under the title "A Modification of the Kolmer Reaction." This title is misleading and should read "A Complement-Fixation Test Using Kolmer's Antigen." This is not a modification of Doctor Kolmer's well-known technic which the writer concludes is the best of all the complement-fixation tests, but merely a system in which the Kolmer antigen is used with excellent results.

The signer trusts that this communication will eliminate any misunderstanding that may have arisen from the title of the paper.

Very truly,

(Signed) F. O. Huntsinger.

TRANSACTIONS

FOURTH ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS

Philadelphia, Pa., May 20, 21, 22 and 23, 1925.

DR. JESSIE W. FISHER, OF MIDDLETOWN, CONN., read a paper entitled **Autopsy Report of Two Cases of Thymic Death During Surgical Operations.** (For original article, see page 241.)

DR. B. S. PARKS, OF PARKERSBURG, WEST VIRGINIA, read a paper entitled **The Bactericidal Action of Whole Blood as Determined by the Heist-Lacy Method.** (For original article, see page 269.)

DR. PAUL ROTH, OF BATTLE CREEK, MICH., read a paper entitled **The Value of Acetone Determination in Expired Air in Correlation with Alveolar Carbon Dioxide Tension.** (For original article, see page 275.)

DISCUSSION

Dr. Frank W. Hartman.—This paper is interesting because it shows what the routine application of any laboratory procedure will pick up as compared with its application only in such cases as it seems indicated. Comparable results are found in the routine application of the Wassermann test as contrasted with its application only where it seems indicated from the history or physical examination.

Doctor Roth spoke of phosphatic acidosis. This terminology is appropriate just at this time since British workers have demonstrated large increases in the inorganic phosphates of the blood in nephritis, using these observations as a prognostic sign. In the few cases of late nephritis which we have observed, the inorganic phosphate content of the blood seems to be of more prognostic value than the creatinine content.

Dr. Paul Roth (closing).—Folin made the statement some years ago that acetone was not responsible for the fruity odor sometimes observed in the breath of diabetics.

In the last stages of severe acidosis a decrease in the amount of acetone in the urine, which sometimes is observed, is a bad prognostic sign, as it indicates that the oxidation of the ketonic acids is still further interfered with and as a result the acidosis is more severe. On the other hand, of course, the diminution or disappearance of acetone in the urine or the expired air, in the absence of acidosis, means improvement.

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EDITORIALS

Principles Relating to the Treatment of Fractures

DURING the past few years numerous articles dealing with the treatment of fractures have appeared. These seem to have demonstrated that operative treatment is not required in the majority of cases. Nonunion due to suppuration, the presence of a foreign body, or interference with normal reparative processes has given rise to a prolonged disability following operative interference in many cases quite out of proportion to that occurring in cases treated by the closed method in which the anatomic results may be regarded as imperfect.

Methods of reduction and maintenance of reduction differ, but certain principles which remain the same must be followed in the treatment of fractures. The following three principles, often neglected, cannot be repeated too often: (1) The long fragment that can be controlled must be dressed in line with the short fragment that cannot be controlled. (2) The mechanism of fractures must be understood, for in the reduction the force must be

reversed and the parts dressed in the reversed position. (3) Immobilization must be maintained for varying lengths of time, depending upon whether compact or cancellous bone or ligaments are involved.

Fractures through the surgical neck of the humerus, through the radius or both bones of the forearm between the attachment of the supinator and the pronator radii teres, and fractures of the femur below the lesser trochanter illustrate the necesity of dressing the long fragment which can be controlled in line with the short fragment which cannot be controlled.

Muscular action is an important factor in the displacement of fragments in these fractures. In fractures of the surgical neck of the humerus the upper fragment is abducted and rotated out by the supraspinatus, the infraspinatus and the teres minor. This fragment cannot be controlled, and the long lower fragment must therefore be dressed in line with it. The aeroplane splint or the old Stromeyer axillary pad answers in these cases, for the lower fragment is abducted and rotated outward somewhat. In fractures of the radius between the attachment of the supinator and the pronator radii teres, the upper fragment will be flexed somewhat by the biceps and supinated by the supinator. It is impossible to control this short upper fragment, and the lower fragment, which is long, should be dressed in supination to bring it in line with the upper, the forearm being flexed to overcome the action of the biceps on the upper fragment. The bones should be dressed in the same position in fractures of both bones of the forearm at this level. Fractures through the radius or both bones of the forearm in the lower fourth offer considerable difficulty for in these cases the pronator quadratus exerts a direct pull, and in fractures of the radius at this level it is difficult to correct the deformity even when the pronator quadratus is relaxed by full pronation. Reduction is especially difficult when both bones are fractured at this level because the pronator quadratus cannot be relaxed, a direct pull being maintained in spite of any position that the fragments can be placed in.

The displacement of the upper fragment in fractures of the femur below the lesser trochanter is typical and constant, the upper fragment being flexed, abducted and rotated outward. The lower long fragment must be dressed in line with the short upper fragment which cannot be controlled. Even when a plate is applied in this fracture the fracture must be dressed in some flexion, with abduction and external rotation. If it is not so dressed, the muscle pull may be great enough to pull out the screws. It makes little difference what kind of dressing is applied in the closed method providing longitudinal displacement of the long lower fragment is prevented and it is brought in line with the short upper one.

The mechanism of the different fractures must be understood if they are to be intelligently treated. It has been repeatedly stated that fractures of the lower end of the humerus are dressed in acute flexion because the triceps acts as a splint, and because it is much easier to extend than flex the forearm if some fixation occurs. These statements are true, but the main reason for acute flexion is that in this position the force has been reversed and the fracture is dressed in the reversed position. Probably about 95 per cent of the supracondylar fractures of the humerus are extension fractures, the line of

fracture running obliquely from above and backward downward and forward. In the extension fracture the force is reversed during the reduction and the parts dressed in the reversed position—acute flexion. Approximately 5 per cent of these fractures are extension fractures, the line of fracture passing from above and in front downward and backward. If this fracture were dressed in acute flexion, the deformity would be increased. This fracture should be dressed in extension, the force being reversed and the fracture dressed in the reversed position.

Reversal of the force—an important factor in the reduction of fractures—is especially well illustrated in Colles' and Pott's fracture. Colles' fracture is a fracture by extension combined with a twist. In reducing this fracture after the fragments are unlocked, the force is reversed, and the hand is dressed in flexion combined with some pronation of the lower fragment. The direction of the force which produced the fracture is merely reversed. The hand when the fracture is reduced falls naturally into flexion with slight pronation. It should be dressed in this position. The same principle applies to Pott's fracture, in the reduction of which the force is reversed.

Cancellous bone repairs quickly and surely. Fractures through the thick part of the neck of the femur, through cancellous bone, repair rapidly; while fractures through compact bone may heal slowly, a higher percentage of nonunion occurring than in cases in which cancellous bone is fractured. Ligamentous repair occurs slowly, and in Pott's fracture, for example, and other fractures where ligaments are involved, immobilization should be continued for a long time.

Experience increases and statistics accumulate which demonstrate the superiority of the modern closed methods, following the principles just discussed, over any operative procedure, which should only be employed when the fragments are so displaced or held by transfixed muscle or tendon that they cannot be brought into line.

David's observations on the fractures of the femur in children are of a great deal of interest and importance. He has shown that compensatory lengthening may occur and is a factor in reducing the necessity of operative interference in these cases. Alignment of fragments to prevent angulation and extension to prevent overriding are of greater importance than end-to-end apposition. Firor has shown that immobilization in plaster of Paris does not give satisfactory results in fractures of the femur in patients over fourteen years of age. The results are good in patients between seven and fourteen; and in children under seven the results are as good as by overhead extension. In adults extension should be applied—skeletal preferably—combined with a Thomas splint and overhead extension.

The principles of dressing the long fragment that can be controlled in line with the short fragment that cannot be controlled; of knowing the mechanism and reversing the force during reduction and dressing in the reversed position; and that different types of tissue repair differently, render the treatment of fractures relatively simple.

—D. L.

The Treatment of Paresis by Induced Fever

SYPHILIS of the brain has long been recognized as an intractable condition and one in which all that could be hoped for as a result of treatment was a symptomatic arrest, due in some measure possibly to the accepted axiom that the more specialized the tissue, the less its ability to repair or compensate for the damage consequent upon trauma or disease.

That such an involvement is greatly to be feared, the character and gravity of the symptomatology amply demonstrates; that the treatment of this type of syphilis is unsatisfactory, the long list of drugs and methods tried renders obvious.

Indeed, so well is this recognized, and so generally is it accepted that once a neurosyphilitic always a neurosyphilitic, that the major aim of the modern treatment of syphilis with its emphasis upon persistence and duration; upon repeated periodic courses of treatment; and upon life-long, periodic serologic examinations is avowedly to protect the syphilitic against and prevent the occurrence of late cerebrospinal involvement,—for we are not yet able to tell when the infection has been absolutely and finally eradicated in any case.

Among the numerous means employed for the treatment of paresis has been the injection of nonspecific substances such as milk, peptone, and other agents as adjuvants to the use of specific remedies, on the assumption of a provocative action upon the dormant foci of the disease with resultant stimulation of antibody production.

Following the observation that in a perceptible number of paretics, in whom there had been a protracted febrile illness, a remission of symptoms occurred, Wagner von Jauregg[1] conceived the idea of deliberately producing a febrile reaction, using tuberculin for the purpose, and in 1909, reported that paretics so treated lived longer and had more numerous and more protracted remissions than a parallel series not so treated.

He later used antityphoid vaccine for this purpose and, still later, observing that the best results occurred in patients having some infectious disease during the nonspecific treatment, proposed the inoculation of paretics with malaria as a pyrexial agent and reported a series of nine patients so treated two years before.[2]

In 1922, the same observer reported that a series of 200 such cases showed evident improvement, fifty having a sufficiently complete remission to enable a return to their previous employment,[3] and, following this report, the use of the method gained impetus with the consequent collection of a rapidly accumulating literature.

Most of the observers thus far have been German, Austrian, or English, but the method is now being used to a limited extent in the United States and a constantly increasing number of reports may confidently be expected.

That remissions occur following the inoculation of paretics with malaria seems indisputable; that they must be carefully evaluated, studied, and interpreted is apparent for, as stated by Solomon and Viets[4] in reference to the evaluation of methods of treatment in cerebrospinal syphilis: "A period of

years is necessary before one can be relatively or absolutely sure that he is not misinterpreting a remission as an arrest."

The treatment of paresis by malarial inoculation is purely empiric and the results without adequate or satisfactory explanation.

It has been suggested that an antagonism may exist between the Plasmodium malariae and the Spirocheta pallida as a result or consequence of which the reaction to malarial infecion brings about a production of antibodies having some degree of effectiveness against the spirochetae, but this suggestion is obviously purely speculative and rests upon no demonstrable basis.

Another view is that, as all the body processes, including those concerned with antibody production, are increased in velocity in the presence of fever, so the syphilitic foci may more actively produce antibodies, but this, also, is purely hypothetical.

Still another hypothesis is that, as malarial parasites are prone to seek lodgment in the minute capillaries of the brain, these vessels are hence apt to become more permeable and so permit protective substances to enter the brain more easily from the blood.[5]

Probably the majority of observers, however, attribute the effects entirely to the high fever induced. The modus operandi, however, remains unexplained for while Weichbrodt and Jahnel[6] found that, in rabbits, a complete disappearance of the spirochetae from scrotal chancres could be brought about by exposure to temperatures of 42° to 44° C. (107.6° to 110° F.), repeated not less than three times, Bunker and Kirby[7] state that the thermal death point of the Spirocheta pallida, "at least, in general paralysis," is 56° C. continued for ten minutes, although the organism fails to grow in temperatures above 40° to 41° C.

The observation of Hines is of some interest in this connection:

Nine days after his arrival from Santo Domingo, a man of thirty-five was admitted to the hospital with typical symptoms of severe malarial infection, the parasites of the aestivo-autumnal variety being found in the blood in large numbers. The cerebrospinal fluid was bloody and gave a strongly positive complement-fixation reaction in amounts as small as 0.1 c.c. Death occurred twelve days after admission. Microscopically, the capillaries of the brain were shown to be plugged with large numbers of parasites which were also found in the adventitial spaces. There were, in addition, definite histologic evidences of syphilis, the lesions, however, showing no signs of alteration as a result of the malarial infection.[8]

It is to be borne in mind, however, that improvement after malarial inoculation takes place slowly and it is possible that this case was too acute to permit such changes to occur, if they do take place.

Despite the fact that the treatment is purely empirical, a sufficient number of cases have now been accumulated to warrant the assumption that the results apparently following its trial are something more than a coincidence; their permanence remains to be seen.

In view of these findings and of the fact that the method may come into more frequent use, some résumé of the proper technic and the contraindications to its use, seems of interest.

The earlier the treatment is begun the better seem the results, but it must be

strongly emphasized that the use of the method is only justified in the hands of skilled and competent workers and where excellent hospital facilities are at hand.

As the main object in view is the induction of repeated attacks of hyperpyrexia, not all cases of paresis are suitable for treatment by malarial inoculation.

Dattner and Kauders[9] consider the method applicable to any case in which there exists no acute or severe chronic disease other than the syphilitic involvement of the nervous system. Patients of low vitality are unsuitable as unable to withstand a sufficient number of paroxysms; severe renal or splenic diseases, or severe and uncompensated cardiac lesions or myocardial degenerations are contraindications. Slight and compensated cardiac lesions are not contraindications but cardiac remedies must be employed in addition to the malarial inoculation.

"Cured" pulmonary tuberculosis is not a contraindication. Obese individuals must be closely watched and this is true, indeed, of all cases because of the ensuing loss of weight and strength, and especially because of the constant danger of delirium. Vigilant and constant supervision, therefore, is essential.

The technic of the inoculation is important as related to the number of successful "takes."

It is necessary that the donor shall have had at least one typical attack. The usual amount of blood injected by foreign workers is 4 cm. by the so-called "combined" method and 2 cm. by the intravenous method.

The "combined" method of injection, "imitating the movements of the anopheles mosquito," comprises the intramuscular, subcutaneous, intracutaneous, and extracutaneous inoculation of the malarial blood.

This is accomplished by introducing the needle at first deeply into the muscles and withdrawing it slowly after each inoculation until the last 15 or 20 drops are injected *on* the skin and inoculated by scarification.

If this method fails, the injection may be made intravenously.

When malarial paroxysms develop, the patient is permitted to have from ten to twelve paroxysms before the course of the disease is controlled by quinine, though some American observers have permitted a greater number in patients in good physical condition.

Occasionally, spontaneous cessation of the paroxysms occur before this number has been reached and in such instances the use of injections of milk or antityphoid vaccine has been suggested to provoke them.

Occasionally, individuals are found who seem refractory to inoculation though, perhaps, this may be due to errors of technic.

It has been stated that, as the multiplication of the plasmodia is asexual in man, as opposed to the sexual cycle in the mosquito, transmission of the disease from inoculated individuals need not be feared and precautions to prevent it are not necessary.[10] Until this is definitely established as a fact, however, careful protection of the patients by screening is advisable.

There is still some disagreement, also, as to whether or not to rely upon the malarial inoculations alone or to reinforce them with the coincident use of specific remedies. This is properly the subject of further experimentation and both

methods will probably require extended and intensive investigation before either can be evaluated.

Finally, it must be recognized that only the lapse of time will suffice to establish the true value of this method of treatment and that in its evaluation, extreme care will be necessary to minimize the effect of the personal equation.

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—*R. A. K.*

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*Results of an American Health Survey**

THE Research Division of the American Child Health Association has made a survey of the health activities of 86 American cities varying in population from 40,000 to 75,000. The work has been admirably done and was carried out simultaneously by four inspectors, each spending at least one week in the city being studied. These cities are graded according to their efficiency in eleven major health activities. These are as follows: (1) vital statistics, (2) control of communicable diseases, (3) venereal disease control, (4) tuberculosis control, (5) prenatal hygiene, (6) infant hygiene, (7) preschool hygiene, (8) school hygiene, (9) sanitation, (10) laboratory, and (11) public health instruction. The cities are divided into upper, middle, and lower third according to the efficiency with which these measures are carried out.

In running over the list one meets with many confirmations of what he might have expected. It is not surprising that such far removed cities as Bay City, Michigan; Butte, Montana; Chelsea, Massachusetts; East St. Louis, Illinois; Muncie, Indiana, and Woonsocket, Rhode Island, are placed in the lower third. For the most part these are manufacturing, mining, or strictly commercial places, many of them having a large foreign population. However, in the list one strikes unexpected figures. It is not surprising that Sac-

*A health survey of 86 cities by the Research Division of the American Child Health Association under the direction of George T. Palmer. Published by the American Child Health Association, 370 Seventh Avenue, New York City, N. Y., 1925.

ramento, San Jose, and Stockton, California, stand in the upper third, but it is surprising that Pasadena is placed in the middle third.

One who knows these California cities simply by short stays as a visitor is surprised at the lack of efficiency in the health work done in Pasadena. On the scale Pasadena stands in the upper third so far as four of the major health activities are concerned and in the middle third measured by seven of these activities. The seven in which this city seems to be deficient are the following: (1) control of communicable diseases, (2) venereal disease control, (3) tuberculosis control, (4) infant hygiene, (5) preschool hygiene, (6) school hygiene, and (7) popular health instruction.

The survey has evidently been well done and the volume will interest all public health workers. It closes with a most interesting chapter on a proposed plan for health activities in a city of 50,000. This plan is not a theoretical one but is practical, and is based on the activities studied in the 86 cities. A similar work for larger cities has been done by the American Public Health Association. It now remains for some agency to take up public health work in rural communities. I am glad to see that there is no attempt to urge cast-iron rules. While certain approximation to public health standards is desirable, absolute uniformity means stagnation. I regard the volume before me as a very important contribution to public health administration.

—*V. C. V.*

BOOK REVIEWS

(Books for Review should be sent to Dr. Warren T. Vaughan, Medical Arts Building, Richmond, Va.)

*The Medical Department in the World War**

THE empyema experience of the U. S. Army during the World War was unique. Knowledge of the proper treatment of this condition was distinctly promoted. Fortunately the advances made in this field have been perpetuated in the volume under consideration. Three hundred and ninety-four pages have been devoted to empyema. This includes its epidemiology, pathology, roentgenology, bacteriology and treatment, particularly surgical. The illustrations, many of which are in colors, are splendidly done. This contribution need not await the next war to be of value in surgical practice.

Perhaps the most spectacular surgical feats of the war were in maxillary facial reconstruction. The surgical aspects of this work are presented with profuse illustrations.

Sections three and four are devoted to ophthalmology in the U. S. and in the A. E. F. respectively. The opportunity for study of unusual eye conditions both traumatic and nontraumatic, was enormous. The reconstruction work is discussed in great detail. We find a large number of colored illustrations of ophthalmoscopic findings.

The section devoted to otolaryngology is the least comprehensive in the volume and is essentially a statistical compilation.

Clinical Biochemistry†

A LABORATORY manual designed primarily for the use of the students of Melbourne University. It covers the ground traversed by the majority of volumes designed for similar purposes. The studies of blood chemistry and of renal function recommended by the author are scarcely as comprehensive as those used in this country. He does not incorporate the Folin-Wu system. Blood sugar is determined by MacLean's method, a very satisfactory colorimetric method which is quite similar to that developed in this country by Haskins and Holbrook. In the blood urea estimation he also uses MacLean's method. Beyond this, studies of kidney function are limited to the MacLean urea concentration test, the estimation of urinary diastase, phenolsulphonephthalein test and the indigo carmine test. The author remarks that the need for a colorimeter in using the phenolsulphonephthalein

*The Medical Department in the World War, xi, Part II. Prepared under the direction of Major Gen. M. W. Ireland, M.D. Surgeon General of the Army. Pp. 827. Cloth. Gov. Printing Office, Washington, 1924.

†Clinical Biochemistry. By Ivan Maxwell, M.D., M.Sc. Cloth. Pp. 124. Price 12 shillings, sixpence. Melbourne. W. Ramsay, 233 Lonsdale St., 1925.

test is a disadvantage to the general practitioner. The ease and accuracy with which a test tube colorimeter may be prepared at a moments notice impels us to question this statement.

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*Diagnostische Technik**

A MOST comprehensive reference work on the technic of diagnostic examination in all of its phases. Edited by Dr. Julius Schwalbe with contributions on special subjects and special methods of examination, from thirty contributors of recognized repute.

The first portion deals with general methods such as history taking, inspection, palpation, percussion, auscultation and exploratory puncture. In the second portion we find a most comprehensive program for clinical anthropologic measurements and studies of general body structure. There follow sections on the technic of roentgen examination, pathologic, histologic examination and of bacteriologic and immunologic studies.

The second section and by far the largest deals with various special methods of examination with such headings as blood, hemopoietic system, chest, heart and circulation, digestive tract, metabolism, kidneys, sexual function, the nervous system, surgery, gynecology, obstetrics, eyes, ears, nose, etc., venereal diseases, general infections, chronic tuberculosis, toxicology and pediatric examination.

This should serve as a very useful reference work.

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*Diagnostische Technik für die arztliche Praxis. Ein Handbuch für Artze und Studierende. Herausgegeben von Professor Dr. Julius Schwalbe Geh. San. Rat. Mit 380 Abbildungen. Papier. Pp. 851. Leipzig 1923. Verlag von Georg Thieme.

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The next annual Convention of the American Society of Clinical Pathologists will be held in Dallas, Texas, April 15, 16, 17, 1926.